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Section of Physical Medicine

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[*March* 14, 1951]

Some Studies on Muscle Tone

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THE object of this lecture is to consider the modern physiological conception of muscle structure, muscle contraction and muscle tone, and the relationship these should bear to our conception and practice of Physical Medicine as it is to-day.

The *concept* of muscle tone seems to be of importance and has often been discussed in relation to physical education, remedial exercises, posture correction, economy of work, and the mechanics of locomotion. In rheumatology it influences our conceptions of contractures, reflex contractions of the muscles, muscle spasms, and the tender, palpable nodules of the muscles, the so-called myalgic spots. The different modern procedures called relaxation have to be evaluated in relation to our knowledge of physiology.

We must be able to analyse this concept before we can select suitable physiotherapy for an individual case.

On this occasion we will consider only the influence of electromyography.

It would seem to me that the following definition includes the primary concept of muscle tone in the light of modern knowledge and contains the fundamental idea of muscle tone as being essentially a "passive elastic tension". We may say, therefore, in relation to muscle tone that all the striated muscles in the normal body are in a condition of slight tension independent of voluntary or reflex stimulation through the motor nerves. The muscles are always in situ stretched a little beyond the length of equilibrium and thus possess a certain passive elastic tension. (Some two-joint muscles may be relaxed almost to equilibrium, if the joints are moved into artificial extreme positions, but this is of less importance in this connexion.)

Hitherto many physiologists have *wrongly* thought this slight tension was due to a reflex activity through the motor nerves. This idea has developed through the years because of the analogy drawn from the experiments on decerebrate animals, and we have been led to presume the existence of a slight sustained contraction, a few motor units working at a time, in relays. This supposed automatic reflex activity and constant reflex contraction have been defined as muscle tone and it has been thought to persist and to determine the resting positions. In most modern textbooks it has been described as a sort of "stretch reflex" similar to decerebrate rigidity. Many of us had considered this presumed reflex tone an active reflex stimulation always present in all striated muscles. We had not sufficiently appreciated the difference between the condition in the decerebrate preparation and the condition in normal individuals in whom the inhibition from the brain of motor reflexes is preserved.

Some authors, however, follow Sherrington, who said in 1915: "Reflex tonus obtains in, and is confined to, those muscles which maintain the animal in an erect attitude", and also "Reflex tonus is postural contraction". Consequently, they left muscle tone out of consideration in the muscles which do not counteract gravity. They discarded the concept of a general tone and spoke only of a postural reflex tone confined to the extensors and the standing position. They ignored the concept of a universal muscle tone.

In 1924 Lidell and Sherrington described the "myotatic" or what we now consider as the true stretch reflex proper. In more detail this explains that if a passive stretch of an anti-gravity muscle is imposed, a number of its proprioceptors are stimulated and their respective motor neurones excited. Increase of the stretch is accompanied by increase in the number of its proprioceptors stimulated, and of the motor neurones excited which supply it. If the stretch ceases, the activity immediately subsides.

Postural reflex tone of the antigravity muscles is now known to be due to this stretch reflex, whereas stretch reflexes of the flexors are of less significance, if of any at all.

In the horizontal position, the postural reflex tone also subsides, but still a certain passive tension persists—as the muscles are stretched a little beyond the length of equilibrium.

In 1929, it was made possible to solve the problem of active or passive tension and to distinguish between passive tensions and active contractions when Adrian and Bronk devised their needle electrodes, which could be inserted into the muscles of human beings, and there pick up the electrical potential variations accompanying the stimulation and activity of a single or of some few fibres. Since then it has been made possible to distinguish between *passive tensions* and *active contractions*. The normal resting muscle presents no potentials whatever, and no evidence at all of any slight sustained stimulation.

"Motor tone" at rest does not exist, passive elastic forces only are the causes of the tensions of the resting muscle.

In Physical Medicine we must not use such terms as "spasms", "reflex contractions", "contractures", "relaxation", or "variations of muscle tone" without taking the results of the electromyographic studies into consideration (Harrel, Mead, and Mueller, 1950).

We must distinguish between "*active*" (voluntary or reflex) stimulation through the motor nerves, and in respect of what we previously considered as muscle tone, the "*passive*" elastic tension and forces.

Firstly, there are two possibilities of which we should be aware. It may be that a certain tonic stimulation exists through the autonomic nervous system. The striated muscles have their direct sympathetic system, and it may have some direct influence on the consistency and elastic properties of the muscle fibres, besides having an influence on the circulation of blood in the muscles, but this activity does *not* give rise to action potentials which can be registered by electromyography.

Again we must not come to any definite conclusions until more knowledge is available of a certain motor system of thin nerve fibres described by Häggqvist (1940), though this again is not known to have any observed effect recorded by clinical electromyography.

Bearing these reservations in mind, we may pass to the more general and important consideration of "passive elastic tension". Every motor stimulus passing the end-plates is accompanied by action potentials, whether the stimulation is voluntary or reflex. Muscle fibres at rest do not show any potential variations. Therefore, electromyography makes it possible to distinguish between the active and the passive forces and tensions.

Let us now try to analyse our daily clinical problems concerning muscle function from this viewpoint.

The passive tensions must be due to the muscle structures as a whole, the active tensions to the contractions of certain muscle structures.

In spite of voluminous literature in recent years concerning the ultrastructure of the muscle fibrils, much remains to be explained.

The studies of Meyer (1924) and Astbury (1939) indicate that the long molecular chains are the ultimate machinery of contraction.

Undoubtedly, the folding and unfolding of protein chains play a role in the *active* mechanical behaviour of the myosin chains during muscle contraction, but even then a *passive* elastic function as well as a plastic deformation must be assumed to result from the effect of stress and strain. The passive elastic processes are also considered to be due to the uncoiling of chains and stretching of "bonds". The plastic processes are regarded as the flow (or slippage) of chains past one another, the so-called shearing.

Both the active and the passive process are influenced by (1) temperature, (2) mechanical deforming forces, (3) osmotic forces, (4) hydrostatic pressure, (5) chemicals, (6) blood circulation, (7) dehydration, and (8) pH. This is known from experiments with artificial myosin threads, and from experiments with isolated muscle fibres.

The degree of *passive* extension and consequent uncoiling of the molecular chains must be influencing the possibility of *active* coiling and contraction. This point reveals the weakness of the apparently clear and simple electromyographic distinction between "active" and "passive" forces.

However, we may be allowed to consider that we have built up from the elements of this background the synthesis of the conception of the passive elastic properties of the muscles, well knowing that these so-called passive elastic forces are variable and may be influenced by the factors mentioned. It is obvious that these passive elastic forces in the fibre must be added to the elastic tension due to sarcolemma and other structures. It is therefore an over-simplification to speak of the "viscosity" and "molecular chains" of the muscle fibre.

We will now discuss what happens to the passive elastic forces, when a muscle is stimulated and contracts.

The tracings of Adrian and Bronk (1929) showed how the contraction of a muscle starts through the arrival of stimuli at one or a few motor units in a rhythm of about 5–6 per

second. Then, as the magnitude of stimulation and contraction becomes greater, more units come into function, and the rates of stimuli reach 30–40 per second, rarely as high as 50. Clinical electromyography with a good apparatus (Fig. 1) reveals the fact that, when it is

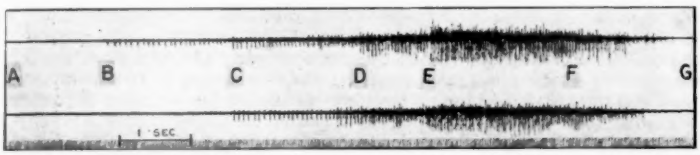

FIG. 1.—Electromyogram from a normal muscle. 2 leads. 2 double channel needle-electrodes. The distance between the two electrode-points is 0·2 mm. In all figures the horizontal line in the time marks one second.

possible adequately to isolate the action of a single motor unit, the individual motor unit discharges normally at a relatively low rate. This refers to and is the same during ordinary movements as well as in ordinary reflexes. Such rate of stimulation is not sufficiently high to cause a tetanus of the single fibre, as seen in artificial stimulation.

In most of our daily volitional muscle contractions and in almost all our reflex movements, the muscle contractions are not tetanic contractions of the units. Even the long-sustained contractions are due solely to a quantitative summation of a number of asynchronously working motor units. Each motor unit contracts at its own rhythm, which is varied with the rate of stimulation. The train of successive impulses and twitches is graded as to frequency and adjusted to the demand of tension. When the contraction is more powerful, fresh motor units are brought into play, and new and higher rhythms are observed.

In most of the muscles the single fibre does not extend the whole distance throughout the muscle from one tendon to the other. At the same time, it is a fact that only as an exception and only in powerful contraction may the fibres be in tetanus, and even then hardly all of them. Consequently, isometric and isotonic contractions are distinct phenomena in isolated fibres. (Moreover, it is evident that the degree of passive extension and consequent uncoiling of the molecular chains must be influencing the active coiling and contraction obtained through stimulation. This fact is, furthermore, the explanation of the different powers and tensions developed in the muscles when they are working respectively concentrically or excentrically and during lengthening or shortening movements. If the molecular chains are thought to be coiled up until maximum before stimulation, further contraction should not be possible. From this, it must be evident that we should not extend direct analogies from experiments on isolated muscle fibres to whole muscles.)

The smoothness of the contraction of the whole muscle, and the delicate gradation shown, are due to the interaction of the active units with the momentarily passive ones, and the resulting force reacting in association with the other passive elastic structures and forces of the muscle and of the passive elastic forces of the natural antagonist.

A fusion of the forces from the successive individual twitch contractions of the different units takes place, and a graded tension is transmitted to the tendons of the muscle.

The elastic properties of muscle conceal and compensate for the rhythmic stimulation found in postencephalitis without tremor (Buchthal and Clemmesen, 1946) and likewise conceal the synchronous stimulation and activity so often found in poliomyelitis and other anterior horn lesions (Buchthal and Clemmesen, 1943). In spite of the rhythmic successive action of the motor units, the contraction of the whole muscle is usually smooth, even if, in some few cases, a regular, fine vibration may be felt by palpation, or heard in the stethoscope.

It is evident, therefore, that we must reckon with the passive elastic tensions and forces in the muscles, and that this concept is much more correct than the now discarded concept of muscle tone.

Our movements take place on a background of passive elastic tensions. These may, depending on the circumstances, assist or resist the movements, and they may be in play as synergists as well as antagonists. They may be and are exploited in economy of work, counteracting inertia and external forces.

Electromyography also demonstrates that quite considerable passive movements may be performed without releasing reflex activity in the muscle itself or in the antagonist, until a certain limit of extension has been reached. In active contraction, the yielding of the antagonist is often quite passive (that is: without stimulation, but not without tension).

In its application to Physical Medicine I shall now analyse the distribution between active and passive forces in the muscles in the horizontal position, in erect position relaxed, in erect position standing at attention, during walking, and during work.

In the supine position, *relaxed in a pool* with gravity eliminated, the joint positions are

determined exclusively by the passive elastic tensions. The average intermediate positions of the joints may easily be determined, and are the same as the so-called resting positions. The average positions are determined through the equilibrium between the different muscle groups and their passive tensions. (If a group of flexor muscles is hypertrophic in comparison to its antagonistic extensor group, the joint in question will adjust itself accordingly in further flexion, and in a case of atrophy the contrary holds.)

In a relaxed position on a bed, the resting positions may easily be determined, when the influence of gravity is taken into consideration. Electromyography reveals that most of the talk of sustained muscle spasms has no meaning. However, Buchthal and Clemmesen (1940) and also Elliott (1944) have shown that in a certain small number of therapy-resistant, long-lasting, tender nodules of the muscles, a certain sustained activity, also at apparent rest, may be found most likely originating in the proprioceptors, and originally caused by continuous hyperfunction to protect a tender part of the body against strain and stress. After some time a sustained activity persists, also at rest, for some reason or other, possibly as a consequence of hyperfunction and fatigue.

Reflex spasms which are, during work or movements, defending a tender part of the body against stress and strain are often exhausting, because of the partially anaerobic conditions for the muscle. They may result in a sustained activity at rest, but usually they do not, and the reflex spasms will disappear, as soon as the patient is placed in a supine position comforted by pillows. This is also the case in acute lumbago and sciatica, in protruding disc, and in the adductor spasms found in hypertrophic osteoarthritis of the hip. Patients with acute muscular affections will, for the most part, avoid stress and strain of the tender parts, and reflex spasms occur in the synergists, in order to protect against movements of the sick muscles. Also these reflex spasms subside when the patient does not move or is placed on the bed.

In most diseases of the nervous system with increased tendon reflexes, and with *spasticity* and *rigidity*, no activity at rest will be found in the horizontal position. Exceptions are: myotonia, Werdnig-Hoffmann's disease, and the fibre activity after acute denervation. The movements which are found in chorea and myoclonia are, of course, accompanied by activity. In the tremor found in postencephalitis and in paralysis agitans, the activity subsides, when the patient is placed so that the end-points of the muscles are brought nearer to each other. On the other hand, the antagonists will often be brought into action through the extension.

The so-called reflex spasms of poliomyelitis are, for the most part, found to be contractures and not sustained reflex contractions (Buchthal and Høncke, 1944). The sensitive, hard muscles which do not yield to passive expanding have lost their elastic properties for some reason or other; we do not yet know how or why. As it may be understood from what has already been said about the elastic forces, there are several possibilities. Why Kenny packings, Priscol, and caffeine have some effect and undoubtedly improve the elasticity of the muscle in passive movements is not known, but may be understood when the different factors influencing the elastic properties are remembered.

When salicylates are so effective against muscle pains, it may be due to the combined effects on the peripheral circulation and on the sensorium. Novocain injections in tender muscles will often stop reflex spasms, which are otherwise found during movements. The novocain injections suppress the activity of the proprioceptors, and with stronger solutions the motor end-plates are also influenced. They stop the pains through their anæsthetic effect, and improve the peripheral circulation through their influences on the vasomotor system. The same result may be obtained by injections along the nerve roots. In this case the result is obtained through an anæsthetic effect upon the roots of the sensory nerves. Quinine lowers the activity of the motor end-plates, while nerve sedatives limit the uneconomic reflex spread of stimulation. This is true also of psychological treatment. Histamine and heat improve the peripheral circulation, and influence the elastic properties in the same way as the other drugs mentioned.

Just these few examples point out how it is necessary in each single case to evaluate and find out which treatment should be preferred, and how the electromyographic results should influence our whole philosophy as to the means of acquiring the correct treatment by Physical Medicine.

Some of the local myalgic spots and nodules of the muscles felt by physiotherapists during massage may be caused by local influence of the many variable factors which determine the elastic properties. (In non-articular rheumatism these possibilities must be reckoned with, just as is the case with panniculitis and with the nodules of the deep fat layers, as described by Copeman and Ackerman, 1944.)

Next we shall discuss the muscle function in standing position and during movements.

The "*relaxed*" *standing position.* The position here is determined and equilibrium obtained by postural reflex tone in association with the elastic forces and in opposition to gravity. If the individual is somewhat excited, the postural reflex tone is more predominant, by reason of a greater and more extensive reflex motor outburst than is usually necessary when

he is at his ease. The same is the case, if he is under influence of strychnine or alcohol, or if some pain exists. With alcohol the central inhibition is partially abolished, with strychnine or pains the central irritability seems augmented.

It appears that we must not transfer deductions directly to ourselves from the results obtained by experiments with the bulbo-spinal preparations. In the decerebrate animal the reflexes occur very easily, and on slight afferent stimuli from the periphery or from the muscles, but *even here a certain amount of afferent stimuli must be present to initiate and sustain the reflex contractions, or else the muscles will relax.* We may presume that it is likely that we are, in daily life, able to exploit the instinctive and acquired reflex mechanisms with the control of our volition superimposed. We initiate and start complicated chains of reflexes (as while walking or driving a car) supervising and controlling the further play of reflexes, interfering only when something is wrong.

We are aware that most of our daily muscle work is done subconsciously (reflex). We are also aware that we are often unable to perform a discrete isolated contraction of our so-called voluntary muscles, a teasing fact during clinical electromyography. Many muscles are out of command, and it differs much from one individual to another, as to how skilled each of us is in this respect.

All our voluntary movements take place on a background of reflexes, but whether the reflexes are brought into action depends on the amount of afferent stimuli and their ability to overcome and break the central inhibition. In normal individuals the central inhibition seems to play an important role, and the postural and other reflexes are released only to the extent strictly necessary as an addition to the passive elastic forces, in order to obtain and maintain equilibrium with gravity, external forces, and inertia.

In the decerebrate animal a slight amount of afferent stimuli is sufficient to start and sustain the chains of reflexes, and every movement will, therefore, take place in a predetermined way, just as the whole posture is influenced. In normal human beings the chains of reflexes will not be released so easily, and they will not dominate the movements and the carriage to the same extent, a fact which has now been shown through electromyography.

In 1942 Seyffarth described how patients were able to *stand in the erect position* without any active stimulation of the calf. Using mostly skin electrodes, Åkerblom (1948) found this to be so, when the weight was over the heels. The quadriceps femoris too was not stimulated when in a comfortable standing position, that is with the knees locked and the line of gravity falling in front of the weightbearing line of the knee-joint. In the lumbar part of the erector spinæ he found only slight activity, if any, whilst during forward bending a strong activity occurred in the same muscle.

In the upright *sitting* position without support of the back, Åkerblom found a certain activity in the lumbar as well as in the thoracic part of the erector spinæ. The activity was considerably diminished and almost disappeared both in the *slack forward sunken* position with the spine in kyphosis and during *backward sloping with support* in the lumbar region or with support both in the lumbar and the thoracic region. (The action of the interarcuate ligaments was mentioned as the main elastic structure limiting the ventriflexion of the lumbar spine in these positions.) These results were confirmed by Floyd and Silver (1950) and Lundervold (1951).

These observations suggest that the postural reflex tone subsides or is suppressed for a while in certain circumstances. This happens as mentioned when the possibility exists of obtaining a state of static equilibrium through bony, ligamentous, and capsular support in extreme positions, where active muscle function is not necessary, while, of course, in addition, the passive elastic forces of the extended muscles must be reckoned with. It must be emphasized that this suppression does not last during muscle work with alternating movements.

The question is now what happens to the postural reflexes in standing position and during trunkbending backwards, forwards, and sideways.

The following investigations were, therefore, carried out to illustrate directly the macromachinery of the human muscles.

For these experiments needle electrodes were preferred to surface electrodes in order to decide if stimulation were present or not. The introduction of the needles causes a little pain, and sometimes a slight activity follows lasting for some few seconds, but soon after quite large movements can be performed painlessly. To avoid pain it is important that the muscle is relaxed during the introduction of the needles, and marked extension of the muscles should also be avoided during the experiments. Very often a standing patient will faint, when he is thus tested, not because of pain, but because of the influence of his surroundings. To avoid this difficulty we used my own back for the experiments, and likewise the backs of some of my assistants and a few brave patients.

At first, it was difficult to interpret the results, but soon some facts emerged concerning the interaction of the muscles. If the muscles of a man standing easy with the feet a little

apart (narrow stride-standing position) are tested electromyographically with needle electrodes, no activity is found outside the postural muscles, and even in these only a slight sustained activity appears. In the quadriceps and in the calf muscles there may be no activity at all. In the two erectores spinæ a slight sustained activity is found, most pronounced in the upper thoracic part. (In the levator scapulæ and in the trapezius, in the latissimus and the obliquus externus abdominis a disturbing short, slight activity may be found occasionally during the deepest phase of a deep inspiration when it is on the point of shifting over into expiration.)

The figures show some curves taken from the erector spinæ of a man standing in a narrow stride-standing position during trunkbending backwards and forwards. In order to get a good reproduction, curves were taken from more than one person. Figs. 3, 4, 5 and 9 from Case I. Figs. 6, 7, 10, 11 and 12 from Case II. Fig. 13 from Case I.

This did not of course affect the observations made of the abolition of reflex activity. As was anticipated, the mechanisms of interaction proved much more constant and less complicated in the sagittal plane than in the frontal plane.

A needle electrode was placed in each erector spinæ at the tenth thoracic vertebra.

Trunk-bending backwards may be done in two quite different ways:

Fig. 2 A shows the fundamental position.

Fig. 2 B shows a low slack trunkbending backwards combined with a bending of the knees and an extension of the hips. The movement is initiated from below. The centre of gravity is displaced forwards, *and the patient yields to the new balance.*

Fig. 2 C shows a high trunkbending backwards combined with straightening.

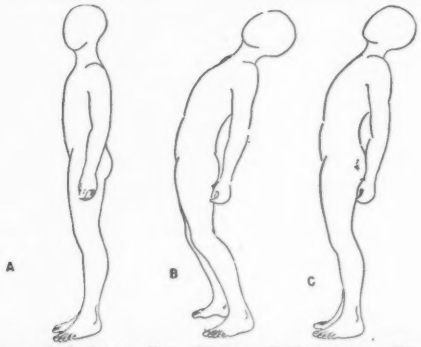

FIG. 2.—A, Normal slack standing. B, Low slack trunkbending backwards. C, Trunkbending backwards.

Fig. 3 shows the curves from a high trunkbending backwards. Electrode a is in the right, and b in the left thoracic part of the erector spinæ. The postural activity is seen, and the activity is raised (A–B and C–D) corresponding to the repeated high trunkbending backwards. The patient does not yield to the new balance, he maintains equilibrium in the position by means of active muscle function.

Fig. 4 shows curves taken in the same starting position with postural activity. By low slack trunkbending backwards (B–C) a complete subsidence of all action potentials takes place. (Only the electrocardiogram persists.) The activity subsides, as soon as the head is inclining, and when the rectus abdominis is extended and brought into play. The bending need not be so deep as shown in Fig. 2 B to make the activity disappear. The main point is that the patient yields to the new balance in hips and knees.

The activity of the erector spinæ reappears, when the patient is asked to return to the original, relaxed standing position. A complete abolition of action potential activity of the postural reflex tone is a fact during low slack trunkbending backwards in spite of the standing position.

Fig. 5 shows the same phenomenon repeated (slack backward bending B–C and D–E). From F trunkbending forwards with raised activity, and still higher activity during erection to the starting position in the last part of F–G. During trunkbending forwards the postural activity is raised through stretch reflexes.

Fig. 6 shows the same phenomenon in another person (Case II) during trunkbending backwards (A–B).

Fig. 7 also shows Case II, A–B during forward bending, B–C during erection, C–D slack standing, D–E slack low trunkbending backwards, all in the standing position.

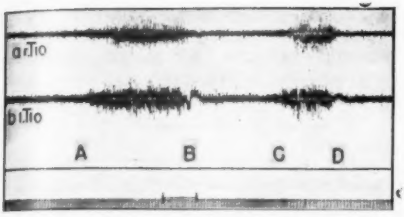

FIG. 3.—a, Right thoracic erector spinæ. b, Left thoracic erector spinæ. Level: Tenth thoracic vertebra. Slack standing position. A–B, C–D, High trunkbending backwards during stretching (Case I).

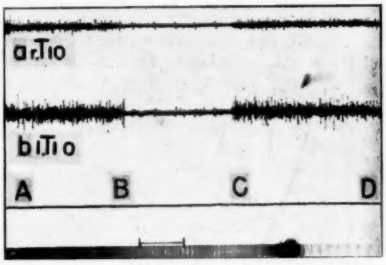

FIG. 4.—a, Right thoracic erector spinæ. b, Left thoracic erector spinæ. Level: Tenth thoracic vertebra. Slack standing position. B–C, Low slack trunkbending backwards. The postural activity subsides. Only electrocardiogram persists (Case I).

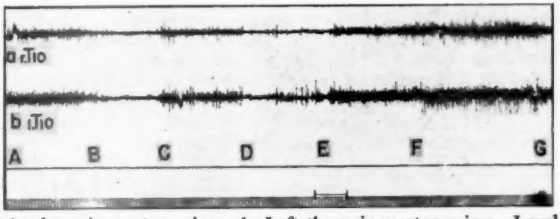

FIG. 5.—a, Right thoracic erector spinæ. b, Left thoracic erector spinæ. Level: Tenth thoracic vertebra. Slack standing position. B–C and D–E repeated, Low slack trunkbending backwards. E–F, Slack standing position. F–G, Forward bending (Case I).

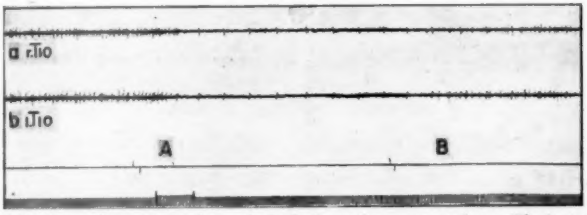

FIG. 6.—a, Right thoracic erector spinæ. b, Left thoracic erector spinæ. Slack standing position. A–B, Slight low trunkbending backwards. The postural activity subsides. Only the electrocardiogram persists (Case II).

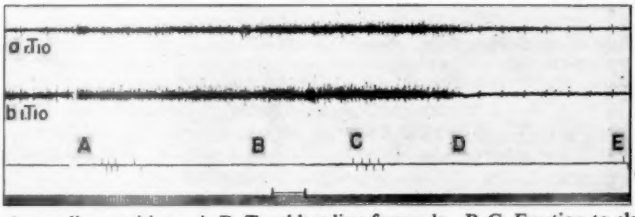

FIG. 7.—Slack standing position. A–B, Trunkbending forwards. B–C, Erection to slack standing position. C–D, Slack standing position. D–E, Low slack trunkbending backwards (Case II).

Fig. 8. Trunkbending sideways may also be done in two ways. In A, a low slack sidebending to the right side is shown, and the sidebending takes place through a displacement of the trunk by means of sideways movements in the hip joints. The movement is initiated from below. The pelvis slides to the left and is tilted to the right, while the trunk is passively bent sideways to the right. The patient yields to the new balance. In B a high sidebending is shown. The patient maintains the positions of hips and knees through active muscle function.

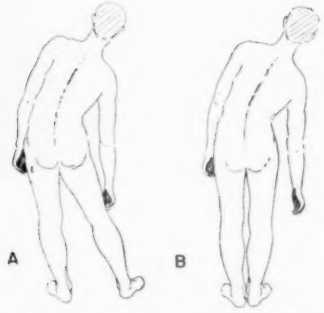

FIG. 8.—A, Low slack sidebending to the right side. B, High sidebending to the right side.

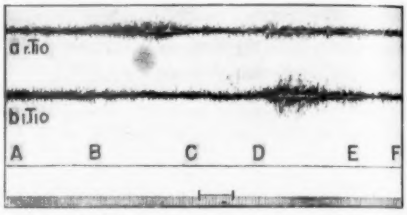

FIG. 9.—Slack standing position. High sidebending. a, Right thoracic erector spinæ. b, Left thoracic erector spinæ. Level: Tenth thoracic vertebra. B–C, Sidebending to the right side. D–E, Sidebending to the left side. The activity is raised in the right erector spinæ during sidebending to the right side, and opposite to the left side (Case I).

Fig. 9 shows the electromyographic results of a high side bending. The starting position is, as usual, a narrow stride-standing position. During sidebending to the right (B–C) the right erector spinæ shows a raised activity; (D–E) during sidebending to the left.

If a low slack sidebending to the right is performed, the postural activity may disappear completely, even in the right erector spinæ, when the extreme position has been reached.

This is shown in Fig. 10 A–B, which was, however, taken in sitting position with one electrode in the thoracic and one in the lumbar part of the right erector spinæ. It may be characterized as a sideways sunken position.

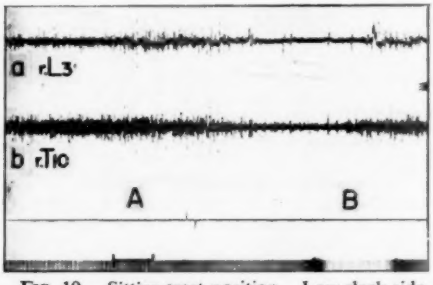

FIG. 10.—*Sitting* erect position. Low slack sidebending. a, Right *lumbar* erector spinæ third lumbar vertebra. b, Right *thoracic* erector spinæ tenth thoracic vertebra. A–B, Sidebending to the right side into a sideways sunken extreme position, where the postural activity subsides almost completely, both in the lumbar and in the thoracic spines (Case II).

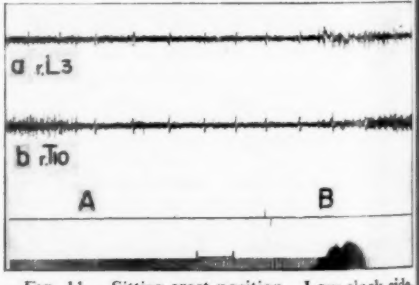

FIG. 11.—*Sitting* erect position. Low slack sidebinding. a, Right *lumbar* erector spinæ. b, Right *thoracic* erector spinæ. Bending sideways to the left side into a complete sideways sunken position. The activity in the right erector spinæ subsides completely during the whole sidebending to the left side from A to B (Case II).

By a low slack sidebending to the left (Fig. 11 A–B) the postural activity in the right erector spinæ may disappear from the first moment, in both the thoracic and in the lumbar part of this muscle. (Sideways sunken position to the left.)

Fig. 12. If the starting position is a standing slight slack trunkbending backwards, the activity subsides as mentioned A–B. From this position a sidebending to the right (B–C) is performed. Through the starting position (C–D) a sidebending to the left side is performed

(D–E). After the starting position has been reassumed (E–F), the patient relaxes into the normal standing position, and postural reflex activity appears in both erectores spinæ (F–G). It can be seen from this figure that in the standing position sidebendings are in this case, performed during almost complete, sustained abolition of the postural activity of the erectores spinæ owing to the simultaneous, slight trunkbending backwards.

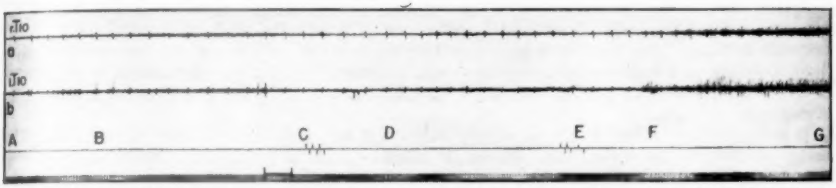

FIG. 12.—a, Right *thoracic* erector spinæ. b, Left *thoracic* erector spinæ. A–B, Low slight slack trunkbending backwards. B–C, Sidebending to the right side. C–D, Reassumption of the starting position in the slight slack low backward bending. D–E, Sidebending to the left side. E–F, Reassumption of the starting position. F–G, Slack standing position. The postural activity is completely suppressed during the low slack backward and sideways bendings (Case II).

It is evident that the technique of bending backwards, forwards, or sideways is quite different when the bendings are performed from sitting position than when they are performed from standing position, because the pelvis is fixed when the patient is sitting down. It is, therefore, much more difficult to carry through a completely relaxed sidebending from the sitting position. On the other hand, it is here less difficult to relax in a forward or in a sideways *sunken* position, that is in extreme positions.

In Fig. 13, the two electrodes are both placed in the right erector spinæ, one in the thoracic, one in the lumbar part. Alternate torsion to the right (A) and left (B) is accompanied by reciprocal function of the two muscle parts here functioning as antagonists.

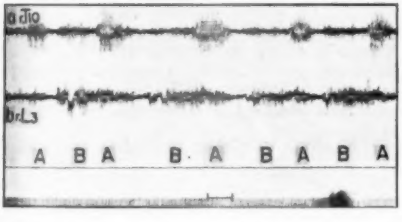

FIG. 13.—Slack standing position. a, Right thoracic erector spinæ tenth thoracic vertebra. b, Right lumbar erector spinæ third lumbar vertebra. A A A A A, Torsions to the right side. B B B B, Torsions to the left side. The thoracic and the lumbar parts of the erector spinæ shown to be antagonists during torsion (Case I).

Experiments in the sitting forward-sunken slack position with lumbar kyphosis confirmed the results of Åkerblom (1948) and Lundervold (1951), that the activity of the lumbar part of the erector spinæ subsided in this extreme position, in spite of the tendency of stretch-reflexes in the erector spinæ during forward bending. Thus it would appear that even the strong postural reflex tone is completely abolished in the extreme forward bent position, in spite of the stretching. This is due to the fact that this position is an extreme position, where capsules, ligaments, joints and passive elastic forces in the muscles are yielding sufficient support. Consequently, postural reflex tone is not necessary in the lumbar part of the erector spinæ. In the upper thoracic part a slight sustained activity persists.

The apparent contradictions of the results determined from patient to patient, and in the same person, are easily explained, when, as here, we consider (1) the different starting positions, (2) the different technique in low and high trunkbending sideways, and in low and high trunkbending backwards and forwards, and (3) the special mechanical conditions in extreme positions with bone and capsule support plus passive elastic forces.

What we had not hitherto realized was that the postural reflexes could be suppressed so completely and so constantly in the standing and sitting positions.

Thus, as part of voluntary movements incurring an active motor stimulation, there is this important feature of the subsidence and abolition of action potential activity of the postural reflex tone.

These experiments seem to prove the reality of a completely local inhibition and an abolition of the postural reflex mechanisms during voluntary muscle work.

If this is right, we may presume a complete inhibition and limitation of the different

reflex mechanisms to the extent which is necessary in daily work for its most economical performance. The passive elastic tensions seem to be exploited to the full, and active contractions set in only when necessary. (When this s true of the trunk muscles, it must be even more important in the muscles of the extremities.)

Most of our muscle work is done through interaction between the instinctive and the acquired reflex mechanism with the control of volition superimposed. Postural reflex tone, Magnus and de Kleijn reflexes, grasping reflexes, &c., are built together in a complicated pattern. Volitional and supervised interference is gradually made subconscious through exercise and use, and is turned into conditioned reflexes, which are released in our daily life according to demand. Gait may be reflex, "relaxed" (that is subconscious), or conscious as in the gymnasium or during a military parade, where the stretching and poise are partially conscious.

It is not sufficient just to speak of relaxation and to prescribe a system of exercises. The term "relaxation", so often used during all kinds of musical instruction, training for sports, &c., has got a completely new and unexpected meaning after the demonstration of the effect of the passive elastic forces.

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Section of the History of Medicine

[*March* 7, 1951]

The History of Acne

By R. N. R. GRANT, M.D.

ACNE cannot be regarded as a serious disease or measured in terms of life and death, but it has a nuisance value out of all proportion to its seriousness, affecting, as it does, young people at an age when they are most sensitive to any disfigurement. It is therefore to be expected that references to acne will occur in the medical or other literature of all highly civilized communities.

Before dealing with ideas on the associations or varieties of acne, it seems pertinent to attempt to trace the origin of the word "acne", itself a problem which has been argued for hundreds of years without any completely satisfactory conclusion being reached.

The ancient Greek physicians certainly recognized acne which they knew as ἴονθοι, a condition which Aristotle [1] describes in sufficient detail for there to be little doubt of the identification. Hippocrates [2] also uses the term, but does not state what he means by it, although his wording suggests that it was a well-known and recognized disease. That ἴονθοι were associated with puberty is implied in the meaning of this word in the singular, ἴονθος, which means "the first growth of the beard".

The early Roman physicians, on the other hand, used the word "varus" which is mentioned by Pliny [3] and discussed briefly by Celsus [4].

For reasons which I hope to make apparent, the meaning of the Greek word "ἀκμή" is important. Previous to the second century A.D. it had a definite medical meaning, to which Galen [5] devotes a whole paragraph, as "the height of a disease", "the crisis of a fever", &c. and is not in any way related to skin disease. However, in the second century A.D. its meaning appears to be widened to include the height or culmination of growth and development and thus "puberty". It is in this meaning that it first appears in relation to "ἴονθοι" in the works of the Greek physician Julius Pollux [6]. The Latin text is not infrequently quoted in later literature but the Greek text seems more significant philologically (Fig. 1).

νίζουσα τὸ κῆρ φύσιν χρῶμα. ἴονθοι, αἰθέμματα ὑυδρακίοις * ἐπὶ τοῦ πρόσωπον, σπυμεῖον ἀκμῆς. ὑπωπία, φακὸν αἷμα τοῦ ὀφθαλμοῦ, συγχύσεις, ὑπόσφυξις. θύμος ὑπερύθρος, ἐρυθρὸς πρόχεια, ἔμπυος, οὐδὲν

phelis, faciei dolor, ſubliuida infeſtatio, naturalem corrumpens colorem. Ionthi, flores cũ * papulis circa faciẽ, vigoris ſignũ. oculis ſubiacentes, lenti legumini ſimiles, cognati ſiue innati. Thymus, ſubrufa ampulla,

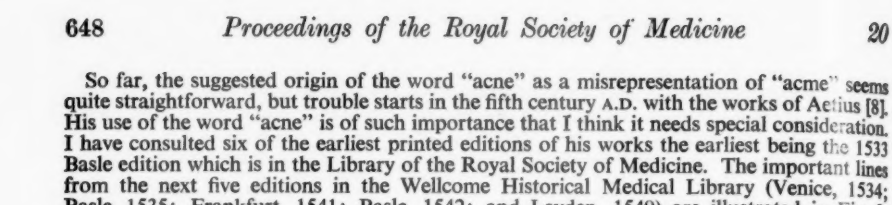
FIG. 1.—Julius Pollux: *Onomasticon, decem libris constans* . . . Frankfurt, 1608, p. 220, 11, 39–43.

Cassius [7], in the third century A.D., goes a little further and explains that since the disease occurs at the "ἀκμή" that is "puberty", the people call it "ἀκμάς" (Fig. 2).

33 Cur in facie vari prodeũt ferè in ipſo ætatis flore vigoréque (quapropter & ἀκμὰς, *id eſt vigores*, idiotarum vulgus eos nuncupat) Hi profectò, vt totã faciẽ

FIG. 2.—From *Medicæ* Art. Princ., Volume 1, 1567, p. 760.

So far, the suggested origin of the word "acne" as a misrepresentation of "acme" seems quite straightforward, but trouble starts in the fifth century A.D. with the works of Aetius [8]. His use of the word "acne" is of such importance that I think it needs special consideration. I have consulted six of the earliest printed editions of his works the earliest being the 1533 Basle edition which is in the Library of the Royal Society of Medicine. The important lines from the next five editions in the Wellcome Historical Medical Library (Venice, 1534; Basle, 1535; Frankfurt, 1541; Basle, 1542; and Leyden, 1549) are illustrated in Fig. 3, reading from above down.



De uaris faciei, qui tum ionthi, tum acnæ Græcis uocantur. Cap. XIII

Vari, ionthi, acnæ. Solet circa faciei cuticulam tuberculum oboriri, paruum quidem, sed durum, quod uari nomine appellatur. Id sanè à crasso humore producitur.

De varis faciei, qui *Græcis* iontho*i* & acmæ vocantur, Cap. XIII.

De uaris faciei, qui tum Ionthi, tum Acnæ Græcis uocantur. Cap. XIII

Solet circa faciei cuticulam tuberculum oboriri, paruum quidem, sed durum, quod uari nomine appellatur. Id sanè à crasso humore producitur. Quare cura

De *uaris faciei, qui tum* Ionthi, *tum* Acnæ *Græcis uocantur.* Cap. XIII.

Solet circa faciei cuticulam tuberculum oboriri, paruum quidem, sed durum, quod uari nomine appellatur. Id sanè à crasso humore producitur. Quare cu

FIG. 3.—Ætius. Tetrabiblion 2, Sermo 4, Cap. 13; *or* De Re Medica, Sermo 8, Cap. 13.

In view of the fact that five out of six early editions have the spelling "acne" rather than "acme" I think the idea can be ruled out that the "n" is a misprint, especially as the Frankfurt edition—the only one with the spelling "acme"—appears to contain other misprints in the next few lines.

The alternative theory that the "n" is there as an early copyist's error also seems untenable, for I am assured that it is a reasonable philological proposition that a copyist or translator, who must of necessity have a working knowledge of the terms involved, is more likely to write a common word in place of a rare word than vice versa. It therefore seems probable, that Aetius himself used the word "acne", this being the first traceable use of this word.

For an explanation of the reason of such a spelling it is necessary to advance a thousand years to the time shortly after the publication of these works. In 1564, Gorraeus [9], who appears to be in no doubt about the distinction between "acme" and "acne", stated that "acne" is so called because it does not itch, suggesting therefore that it is derived from the Greek "α" as a prefix to a contraction of a "κνῆσις" or other similar words meaning "scratching".

Most writers since this time have taken one or other of these two apparently incompatible views as to the origin of the word "acne". A further suggestion has been that it originates from the Greek word "ἄχνη" ("anything that comes off the surface") but I have not been able to find any historical support for this.

Although I make no claim to be a philologist I would like to take a middle course in this matter and offer a suggestion: We know from Cassius [7] that the word "ἀκμάς" was first used as a lay term and thus may not have had any official spelling. Such a situation might have resulted from its adoption into spoken Greek from a foreign source. Subsequent attempts to fit it into Greek medicine could have resulted in a variety of spellings, each with its rational explanation.

Historical and geographical considerations suggest Ancient Egypt as a possible source, bearing in mind the Greek domination of Egypt for the last three centuries before Christ and the attention paid there to medicine in general and skin conditions in particular. When I discovered that they had a word "aku-t" which occurs in the Ebers Papyrus [10] and elsewhere and is translated by Budge [11] as "boils, blains, sores, pustules, any inflamed swelling" (Fig. 4), I felt that the similarity was too close to ignore.

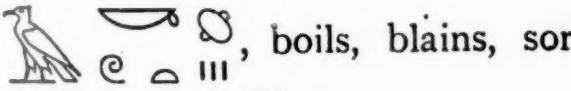


FIG. 4.—Budge, Sir E. A. Wallis. An Egyptian hieroglyphic dictionary. London, 1920, p. 11. Aku-t.

I thought it might be worth while to compare the prescription for this condition given in the Ebers Papyrus with some Greek prescriptions for acne, but unfortunately the Egyptian Pharmacopœia of the time appears to contain largely ingredients of animal origin, whereas the Greek contains mainly vegetable preparations. There is one common factor in honey, but as this is so frequently used in both countries I cannot offer it as confirmatory evidence.

Turning now to the associations and varieties of acne which have been recognized, I feel obliged to include a few words on rosacea, the history of which is inseparably intertwined with that of acne.

The earliest reference to a condition which may have been rosacea has been pointed out to me by one of my colleagues, Dr. Ida Macalpine [12]. I refer to the Mark of Cain which is mentioned in the Fourth Chapter of Genesis and was probably written about two thousand years B.C. I am assured by a minister of the Church that such an idea does not conflict with any established opinion of the Church. Certainly, by earthly modern standards, Cain had good reason to have the feelings of guilt and shame which are now recognized as important ætiological factors.

The early Greek and Roman writers seem to confine the terms "ionthoi" and "vari" to a condition occurring at puberty and therefore probably limited to acne vulgaris as we know it, and not including rosacea.

Theocritus [13], in the third century B.C., may have been describing rosacea when he mentioned the pimples on the nose said to be caused by telling a lie, and for which he uses the word "ψεῦδος". This word elsewhere was used to mean "a lie" but the meaning here is explained by the Scholiast, who uses the terms "ionthoi" and "psydracion" to describe the lesions.

The earliest suggestion that "ionthoi" might include more than one disease was made by Galen [14] who gave different prescriptions for two kinds of "ionthoi" in one of which the nodules were harder than the other. The same distinction is made by Paulus [15] in the seventh century A.D. who prescribed honey for the softer lesions and a mixture in a soap basis for the harder lesions. Neither Galen nor Paulus gives an adequate clinical description to allow identification of these two types in modern terms.

A good clinical description of rosacea occurs in Chaucer in his sketch of the Somnour in the Prologue to the Canterbury Tales.

A somnour was ther with us in that place,
That hadde a fyr-reed cherubbines face,
For sawcefleem he was, with eyen narwe.
As hoot he was and lecherous as a sparwe,
With scalled browes blake and piled berd;
Of his visage children were aferd.
Ther nas quik-silver, litharge ne brimstoon,
Boras, ceruce, ne oille of tartre noon,
Ne oynement that wolde clense and byte,
That him mighte helpen of his whelkes whyte,
Nor of the knobbes sittinge on his chekes.
Wel loved he garleek, oynons and eek lekes,
And for to drinken strong wyn red as blood.
Prologue, 623–635.

This passage is also of interest in showing that the pharmacological armamentarium of those days did not differ significantly from that of to-day and that Chaucer recognized the association with, or aggravation by, spicy foods and strong drinks.

The conception of rosacea as a permanent blush is given by Falcutius [16] about A.D. 1400, whose words I would like to quote from the English translation of Daniel Turner: ". . . and deduceth the cause from a hot but viscous and thick blood generated by some intemperies or vice of the liver, which being brought by the capillary arteries to the surface of the skin of the face is there diffused as happens in blushing, but by reason of its lentour or clamminess not being returned as it ought presently by the veins, stops therein and causeth redness, which neither yet being capable to be discust by reason of the density of the cuticle, raiseth

the same up into little pustules, and at length ulcerates, having vitiated the frame of the cutaneous glandules by its long stagnation."

Rhodiginus [17] has clearly been influenced by the Scholia of Theocritus and thus seems to confuse rosacea and acne more than other sixteenth century writers.

The sixteenth century seems to have produced several penetrating observations from which I have selected four written in English. Sir Thomas Elyot [18] in his *Castell of Helth* describes a condition, due as he says, to an abundance of melancholy blood in which he associates adiposity of the upper part of the body with boils, much urine, and "black poushes"—one wonders if he had seen acne in association with endocrine dysfunction.

Nicholas Udall's translation of the Apophthegmata of Erasmus [19] contains an interesting note which shows once again the relationship of rosacea to shame.

> The oratours and aduocates (who wer had in high price and estimacion in Athenes) he called the common droudges and pages, of euery Iacke and Gille, for that thei wer of force constreined, to speake all that euer thei did, to please men, and euen like bonde slaues, to flatter the beastlie foolishe rable of the people. And the assembles of the people, swarmyng about the same orators, he called the pimples or little wheales of glorie.
>
> ¶ The Greke word that he vsed, was ἐζανθήματα, that is, little pimples or pushes, soche as of cholere and false flegme, budden out in the noses and faces of many persones, & are called the Saphires & Rubies of the Tauerne.
>
> Mening thereby (as I suppose) that like as soche pushes in the visages of men, are angrie things and greffull, and also finall discomfort to the parties, that the same may not for shame shewe their faces, but hiden theimselfes, and refrein to come in compaignie: so the frequent assembles of people, swarming about oratours, doe finallie purchace and conciliate vnto the same moche enuie, displeasure, hatered, trouble and vexacion, ensuyng of the glorie that thei haue in the beginning. As chaunced to *Demosthenes*, and to *Aschines* in *Athenes*, and to *Cicero* in Roome.
>
> 6. Frequente assemblees of the people gatheryng about the oratours been the pymples of glorie.
>
> *From* Udall, Apophthegmata of Erasmus. The I Booke, 79.

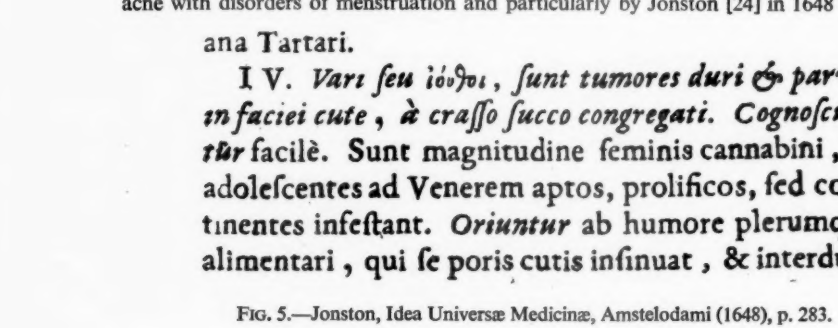
Although he is discussing the meaning of the Greek word "ἐζανθήματα" there is no doubt that he is referring to rosacea when he talks of "the Saphires and Rubies of the Tauerne".

Andrew Borde [20] in his Breviary draws attention to the dietary associations of rosacea.

No summary of this period of history could be complete without a quotation from Shakespeare [21]. Here is Fluellen's description to King Henry V of " . . . one Bardolph, if your Majesty know the man: his face is all bubukles, and whelks, and knobs, and flames o' fire".

Turning to the seventeenth century and returning to medical writings, Sennert [22] is certainly the most frequently quoted. He follows the line of thought of Theocritus and Rhodiginus, deals with acne and rosacea under the same heading, and distinguishes himself by pointing out how difficult these conditions are to cure.

Some more constructive remarks were made by Riolanus [23] in 1638 who associated acne with disorders of menstruation and particularly by Jonston [24] in 1648 (Fig. 5), who


ana Tartari.

I V. *Vari ſeu ἰόδοι, ſunt tumores duri & parvi, in faciei cute, à craſſo ſucco congregati. Cognoſcuntur* facilè. Sunt magnitudine feminis cannabini, & adoleſcentes ad Venerem aptos, prolificos, ſed continentes infeſtant. *Oriuntur* ab humore plerumque alimentari, qui ſe poris cutis inſinuat, & interdum

FIG. 5.—Jonston, Idea Universæ Medicinæ, Amstelodami (1648), p. 283.

linked acne with a pattern of heterosexual behaviour in a manner very close to modern psychosomatic ideas on the subject. His words are translated by Culpeper as: "Vari are little hard tumours on the skin of the face curdled up of an hard thick juice. They are known easily. They are of the bigness of a hemp seed, and they infect young people that are inclined to venery and fruitful, but chast withal and continent."

One gets the impression from Daniel Turner [25], writing in 1714, that most physicians of the time considered the treatment of such minor conditions beneath their dignity, but in the latter half of the century these diseases are made to fit into the elaborate classifications which were then becoming popular. Sauvages [26] following the ideas of the Theocritus, Rhodiginus, and Sennert approach to the problem, is doubtful about including the Gutta Rosae of wine bibbers in the same category as ordinary acne.

The Gutta Rosacea (or Rosae) is subdivided into nine types by Plenck [27] in 1783, who deals only very briefly in a separate Chapter with Vari seu Ionthi. His brevity, however, is not without point for in his second edition he adds the categorical statement "Matrimonium varos curat".

Passing into the nineteenth century the first to be considered must be the fathers of modern dermatology, Willan and Bateman [28]. They divide acne, in the sense of Ionthoi or Vari into three types, simplex, punctata and indurata on the basis of three types of lesion which occur. A fourth member of this group of diseases they call acne rosacea which they agree is the Gutta Rosae or Gutta Rosacea of the older physicians. Willan and Bateman are the first to apply the word "acne" to this latter condition while realizing at the same time the essential differences between it and the other three members of the group. The first three are regarded as local lesions to be treated by local remedies whereas acne rosacea is regarded as symptomatic of disorders of function of the liver or stomach.

During the next few decades the literature on acne becomes voluminous, with division of opinion particularly on the subjects of classification and nomenclature. There is argument as to whether the primary lesion of acne is a pustule or a papule; whether all pustular conditions of the face should be called acne; whether it was necessary for any lesion to have a red areola for it to qualify for the name acne, and so on.

They all agree, however, that the condition is primarily a disease of the sebaceous glands. They cite with varying emphasis and elaboration the predisposing factors and associated conditions mentioned by other and earlier writers. These factors, of which Baumès [29] makes a comprehensive list I may summarize as: constitutional factors, mode of life, use of cosmetics, affections of the alimentary tract, menstrual abnormalities, and supposedly abnormal sexual behaviour.

A new suggestion was made in 1842 by Gustav Simon [30] who considered the disease to be primarily of the hair follicle as distinct from the sebaceous gland, and who was also one of the first to discover the "acarus" or "demodex folliculorum" which he thought might occasionally be an ætiological factor. This acarus was very thoroughly studied by Erasmus Wilson [31] who was convinced that it played no part in the ætiology of acne. Nor did Erasmus Wilson [32, 33] accept Simon's views on the idea of the hair follicle being the seat of the disorder. In supporting the opposing view that the sebaceous glands were disordered he referred to the normal lubrication of the skin by the sebum and states: "But in the inhabitants of cities and towns in the midst of the sedentary and irregular habits of refined society, and of the mental wear and tear of practical life, such a state of the unctuous system of the skin as I am now describing rarely or never exists."

Of those who differed from Willan and Bateman in the matter of nomenclature I will mention only Fuchs [34], who in 1840 divided acne into Acne Vulgaris, Acne Mentagra and Acne Rosacea. This being the first use of the term "Acne Vulgaris", a term which has persisted to the present day.

It is in the voluminous chaos of the middle of the nineteenth century then that I propose to leave the subject of the history of acne. In conclusion perhaps I may summarize subsequent developments. The discovery towards the end of the nineteenth century of the acne bacillus paralysed all other research on the subject for about thirty years. The first real rays of light began to fall when Bloch [35] in 1931 proved conclusively the relationship of acne to puberty. Since then much has been achieved in confirming the views of seventeenth century and earlier physicians in modern scientific language, and by modern scientific technique. May I add that my own humble contribution to the problem [36] has been to elucidate the relationship between "ionthoi", or acne vulgaris, and "ionthos", the first growth of secondary sexual hair, a relationship which was obviously recognized by the ancient Greek physicians two and a half thousand years ago.

I wish to acknowledge with gratitude the kind co-operation of the Librarian and Staff of the Wellcome Historical Medical Library in the preparation of this paper and the accompanying photographs.

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A Note on the Dental Key

By SIR FRANK COLYER, K.B.E., LL.D., F.R.C.S.

THE first knowledge we have of the dental key is in a paper published by Alexander Monro in 1742.[1] Monro describes it as "another instrument for drawing teeth" and it is not until 1754 that the word key appears in print and then under the name "Clef Anglaise" in a work by Lecluse.[2]

The instrument illustrated in Monro's paper is shown in Fig. 1. It consists of a metal shaft fixed in a wooden handle, at the end of the shaft is a projection to which a claw is attached by means of a screw. Monro states that the instrument as received by him from Dr. John Fothergill of London had a metal handle and that he

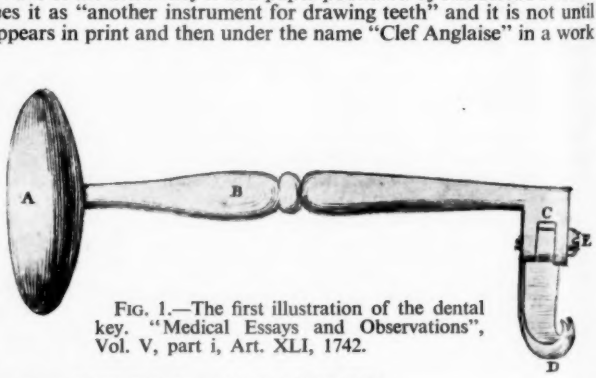

FIG. 1.—The first illustration of the dental key. "Medical Essays and Observations", Vol. V, part i, Art. XLI, 1742.

[1] *Medical Essays and Observations* (1742) Vol. V, part i, Art. XLI. Edin.
[2] *Nouveau Elemens d'Odontologie*. Paris.

replaced it by the wooden one of a gimlet shape. This is an important piece of information because it tells us that the first key of which we have any knowledge was made entirely of iron. The key, as shown by Monro, is neatly constructed and it is unlikely that it is representative of the earliest stage of the instrument as there are several examples in museums of keys of a much more primitive character and with open handles similar to those of many common keys.

An early stage in the development of the key was the addition of a metal projection to the shaft on the side opposite to the claw, the latter being swung from the shaft. This piece of metal became known as the bolster and was the part which rested on the gum and formed the fulcrum. We have no idea when the addition was made but it is found in early examples of the instrument and is shown in A. L. B. Jourdain 1760.[3]

The second illustration of a key is in a French work by M. Bourdet (1757).[4] In this instrument the end of the shaft has a slight double bend and the claw is screwed into a piece of metal fixed to the projection from the shaft. Bourdet himself calls the instrument a lever which he formed on the English key.

The next publication bearing on the history of the key is Perret's catalogue (1772), where there are illustrations of two useful alterations. The first is an arrangement which allows the claw to be used for the right and left sides without unscrewing the attachment to the shaft. This alteration, which was made by Garengeot, consisted in constructing the portion carrying the claw so that it could rotate in the head of the shaft, the position being fixed by a spring-catch attached to the body of the instrument. This method of carrying the claw on a swivel was improved upon by later authors. The second illustration shows an alteration introduced by Perret and consists in fixing the claw by a sliding rod within the shaft. A feature of one of the keys in Perret called by the name of Frère Côme is the handle, which is in the form of an elevator and can be unscrewed and used to lift the tooth from the socket after it has been raised with the key.

An important stage in the evolution of the key was introduced by R. Clarke (1795).[5] The direction in which a tooth is removed by the key is in a curve at a right-angle to its axis of motion, and this, according to Clarke, is to be found by drawing a line through the point where the bolster rests on the gum and the middle of the handle. A disadvantage of the key with the straight shaft when used on the inner side of the teeth is that the axis of motion is in an oblique direction and there is therefore a tendency for the tooth to be pressed against the one immediately posterior. If, however, the shaft is given a bold double bend the axis of motion is in a straight line through the bolster and the middle of the handle and the tooth can be removed in a curve at a right angle to the line of the arch. The introduction of this marked double bend in the shaft was a great step forward in the development of the key.

In all the keys which had been illustrated up to 1795 the claw could be used in one position only. Spence, the friend of John Hunter, had the shaft extended to allow the claw to be fixed in advance of the bolster. This was a distinct improvement as it allowed the bolster to be placed on the tooth anterior to the one to be removed. In cases where there was suppuration in the bone this was a great advantage as the bolster could be placed on an area comparatively free from tenderness. Fox in 1806 made provision for the claw to be used behind the bolster as shown in Fig. 2, which is a picture of his key.

During the next thirty to forty years changes were made in the key principally in the shape and size of the bolster and the introduction of contrivances to adjust the claw without the need of placing the finger in the mouth, but few of these modifications left a permanent mark on the character of the key. The alterations in the form of the bolster were designed with a view to minimizing the pressure on the gum. They did not always succeed in their object and this was particularly the case with the one introduced by T. Hardy in which the bolster was made sufficiently long so that the ends, which were padded, rested on the neighbouring teeth and so took the pressure off the one to be extracted. In theory the idea seemed a good one but in practice the results were stated by other authors to have been far from satisfactory as the pressure being transferred to the neighbouring teeth resulted in a tendency for them to be dislocated.

The key was a favourite instrument with practitioners for well over one hundred years but fell into disuse when forceps were introduced with beaks fashioned to fit the necks of the different classes of teeth. It continued, however, to be advocated by Garretson in his *System of Oral Surgery* (Philadelphia) as late as 1890 for the removal of certain teeth and Mrs. Lindsay informs me that it was used by a well-known practitioner as late as the early part of this century.

[3] *Traités des Dépôts dans le sinus Maxillaire, des Fractures, et des Caries de l'un et de l'autre Mâchoire; suivis De Réflexions et d'Observations sur toutes les opérations de l'Art du Dentiste.* Paris, Plate VI.

[4] *Recherches et Observations sur toutes les parties de l'Art Du Dentiste.* Paris, Plate IX, Fig. 5.

[5] *Medical Facts and Observations.* London, Vol. VI, p. 123.

Although nothing is known about the origin of the dental key it is possible that it may have been suggested by the common key. The similarity of some of the old forms of the latter to the early dental instruments is most striking as may be seen from the key illustrated in Fig. 3. Compared with the instrument shown in Fig. 1, the part above to the right of the

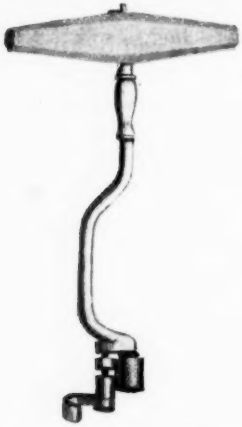

FIG. 2.—The dental key as modified by Fox.

FIG. 3.—An example of a common key, date about the early part of the eighteenth century.

arrow corresponds to the projection from the shaft, the part below to the left to the claw. If a division were made at the position of the arrow and a hinge inserted, then it would be possible to use the key as an instrument for extracting teeth. That the key may have originated in this way is perhaps not too fanciful an idea, for the forceps are but a modified pair of pincers and the pelican was suggested by the instrument used by coopers to bind hoops on to barrels.

The view that the common key was probably the forerunner of the dental instrument is referred to by P. B. Goddard and J. E. Parker (1832)[6] and they state on the authority of a friend that the famous surgeon of Cairo, Clot-Bey, was in the habit of taking out molars by means of a common key and a piece of twine, an operation he performed with great dexterity and rapidity. L. Koecker (1826)[7] on the other hand regarded the key as an improved form of the pelican and other authors have described it as a combination of the davier and pelican.

There is no unanimity among writers about the original home of the key. It is called "The English key" by the French writers Perret and Jourdain; J. R. Duval, also a Frenchman, refers to an improvement he made in the "The English key", and C. Manicus in a German publication remarks that "The English key is used more frequently than any other instrument". The Italian writer Soldo illustrates and describes an instrument which he calls the English, or Fothergill's key, and Arroyo the Spaniard gives an illustration of the English key. Andrée, whose book was published in Leipzig calls it the English key and the German writer Bücking describes and illustrates the English key. The French authors Laforgue and Désirabode speak of Garengeot's key while Lefoulon uses the words "key of Garengeot, or English key". Gariot also gives the name "key of Garengeot" to an instrument which is similar to the one Perret describes as the English key. To add to the difficulties of unravelling the origin of the key we find in Serre that the instrument generally known as that of Frère Côme is named a "Lever with a cross-handle" and that the instrument he calls Garengeot's key is not like the form shown in Perret. On page 252 of Serre's work we read "This instrument (Garengeot's) is often called Frère Cômes' key". Serre says that he cannot understand why in France it is called Garengeot's key as that author does not mention or illustrate it in his works. He adds the remark that "the inventor of the key is unknown". Gerbaux seems to have no doubt about the home of the key, for he tells us that "the key of Garengeot, generally named the English key, is the instrument the most in use to extract the grinders, except in France, where in fact, it originated".

[6] *The Anatomy, Physiology and Pathology of the Human Teeth.* Philad., p. 101.
[7] *The Principles of Dental Surgery.* London, p. 308.

The date of the invention of the key is not known. The first illustration, as already mentioned, is in "Medical Essays and Observations" (1742). Lecluse in his "Nouveau Elemens d'Odontologie", which was published in 1754, says "You can use the Pelican which Garengeot has formed on the English key and which I have altered twelve years ago". In a footnote he adds "An instrument which Dentists use in England". Bound up with the copy of this book in my possession is a small work on the teeth of children by the same author. At the end of the book is a letter from M. Bagard approving the manuscript of "Nouveau Elemens d'Odontologie". If the printed word is an exact copy of the manuscript then we have evidence that the key was known to Lecluse in 1740 and to the English before that date.

The key was probably unknown to Garengeot when he published his book in 1725 as he does not include it in the list of dental instruments he described and illustrated. It was, however, known to him at a later date and he introduced certain alterations which led to the instrument being called by his name and his being regarded by some writers as its inventor. Fauchard (1728) makes no reference to the key although he deals in detail with the elevator, pelican and forceps. The absence of any reference by either Garengeot or Fauchard would seem to indicate that the key was not generally known in France during the second decade of the eighteenth century. The key is not illustrated in Heister (1719), which may be regarded as a representative German work on surgery of that period and it is not mentioned by Mangetus (1721).

When we turn to English literature we find that there is no mention of the key in William Salmon's *Ars Chirurgica* (1799). "The Mullets and Forceps for drawing of Teeth" which are illustrated are copies of those in Scultetus and Paré. Referring to the operation of extraction of a tooth he states that "The Gums must first be opened with a *Fleam*, and the Flesh loosened round about the tooth, *Then done, you must with Pincers, half-Pincers, Punches, or a Pellican, lay hold of the Tooth, and with a wary and gentle kind of forcing bring it forth.*"

In a paper by Sir Ambrose Heal on "Cutlers Trade Cards" there are some interesting data which have a bearing on the date of origin of the key. These cards were "not paste boards but were engraved and printed on open sheets of good paper" and their purpose was primarily that of advertisement. Reproductions of eleven "cards" are included in Sir Ambrose's paper and seven of these have drawings of dental instruments, the double-ended pelican and forceps of the paces and crow's-bill patterns are represented but not the key. The dates of the "cards" are given by the author as from the last decade of the seventeenth century to about 1730. It is fair to assume that the instruments portrayed were those in general use at the period and as the key is not shown, it either had not been introduced or was but little known.

Evidence of a negative character is afforded by the case of surgical instruments purchased by The Company of Barber-Surgeons of Newcastle upon Tyne in 1703. The dental instruments in the case are a Douglas lever, a pair of forceps of the crow's-bill pattern, a double-ended pelican and an elevator; the key is not included.

Amongst the plates in a book by C. Bew (1819) is one depicting several old types of instruments for extracting teeth and amongst these is a very primitive form of key. At the end of the description Bew states "This instrument was in use in the reign of Queen Anne". This remark makes the absence of any reference to the key in the works of Heister, Mangetus, Garengeot and Fauchard difficult to understand, for if the key had been invented before they wrote it seems incredible that all four should have omitted any reference to it and I think raises the question whether the information in Bew is reliable. There seems to have been some confusion in the mind of the author about the nomenclature of instruments, for example, the double-ended pelican is called "an instrument of the key species", and one somewhat like the instrument, called by Fauchard a lever, Bew describes as "An antiquated key instrument with a sliding rod". There is no evidence to support his statement and there is a certain amount of looseness of expression in some of his writing.

Disregarding this statement in Bew, and taking into consideration the available evidence, I am inclined to put the invention of the key to about the first half of the third decade of the eighteenth century.

[*May* 2, 1951]

Andrew Ure, M.D., F.R.S. (1778–1857)

By W. S. C. Copeman, O.B.E., F.R.C.P.

Andrew Ure, M.D., F.R.S., was one of those brilliantly versatile men of science of whom the end of the eighteenth and the beginning of the nineteenth century furnished a number of examples. Under the denomination of Natural Philosophy they assembled an encyclopædic

understanding of the triad of infant sciences, chemistry, physics and mechanics, upon which the foundations of the Industrial Revolution were, with their help, built.

He was born in Glasgow on May 18, 1778, the son of Alexander Ure and Anne Adam, and was educated at the Universities of Edinburgh and Glasgow, taking his M.A. in 1798–99 and his M.D.Glas. in 1801. He became a Member of the Faculty of Physicians and Surgeons, Glasgow, in 1803. He died on January 2, 1857, at 18, Upper Seymour Place, London, the residence of his son Alexander. He married on December 26, 1807, Catherine Monteath, daughter of the Rev. John Monteath of Houston, from whom he appears to have separated about 1819. They had two sons, Andrew who studied at Glasgow University but did not take a degree and who died unmarried in China about 1840, and Alexander, later F.R.C.S.Eng., the first surgeon to be elected to the staff of St. Mary's Hospital, London, after its foundation in 1854; he died unmarried as the result of a fall from his horse on June 13, 1866. His only daughter Catherine married Thomas Mackinlay, F.S.A., a noted antiquary and collector, whilst still under age in 1837.

Andrew Ure was well known in his day as an innovator of popular scientific teaching, and as a pioneer in the application of scientific principles to the Arts, industry and the manufactures. As *The Times* said in his obituary notice (1857): "The teaching of the application of chemistry to the Arts and manufactures has since been introduced into almost every University and into many public institutions. To Dr. Ure belongs the honour of having taken the lead in a movement which has had incalculable power in the development of the national wealth, and of promoting the interests of both science and art. . . . The influence which in early life he exerted as a teacher he continued in later years as an author. . . . No works have done more for directing and extending the application of science in the ordinary uses of life."

Dr. Andrew Ure, F.R.S.
(From the water-colour painting in the National Portrait Gallery, London. Reproduced by permission.)

Work at Glasgow

As a student he attracted notice from the exercise of a critical faculty, which was more admired in later life, and he won the University Prize for Anatomy with an essay on hernia. After qualification he joined the 7th Regiment of North British Militia as surgeon, and went for a period of training to Fort George, where his Colonel was George, 4th Earl of Glasgow, who became his patron and close friend throughout life. He shortly afterwards was posted to Elgin, where he evidently gained the goodwill of the inhabitants since the Freedom of the Borough was shortly conferred upon him "for the particular favour and esteem that the Provost, Baillies, Council and community have and bear for Captain Andrew Ure". The Regiment was disbanded in 1803 after the Peace of Amiens, and he settled in private medical practice in Glasgow. In 1804, at the early age of 26, he was appointed as Professor of Natural Philosophy and Chemistry at the instigation of his predecessor in the Chair, Dr. George Birkbeck, also a medical man, who had decided to transfer to London. Dr. Birkbeck subsequently founded the first "Mechanics' College" in England (later Birkbeck College) on the plan of the Andersonian Institution. He also became a Founder and Councillor of University College, London. Dr. Ure accepted the Chair at Glasgow on somewhat unusual conditions which were the result of the low financial circumstances in which the Governors found themselves: "The Professor is to look for no further salary than the proceeds of the various courses, and is to defray all necessary expenses", and to provide his assistant "in a suitable compensation". Such was the popularity of his teaching, however, that in the next year we find that the audiences for his popular science lectures numbered 400–500 every quarter. Tickets of admission to each course cost 5s. Sir William Hooker, the great botanist, speaking for him when he was a candidate for Fellowship of the Royal Society, reported that: "He has a great and judicious command of language; his delivery is clear and animated and

forciful; he displays a most thorough knowledge of the subjects of which he treats, and he illustrates these subjects by the most successful experiments." He also added of his fellow Scot that "His pronounciation is free of all national peculiarities"!

In 1800 (Sir) Humphry Davy had published his "Research Concerning Nitrous Oxide and its Respiration", a work which it is now generally recognized led up to the introduction of anæsthesia nearly fifty years later. He induced many of his friends, of whom Dr. Ure later became one, to inhale this gas and record their sensations. It may be interesting to quote part of the latter's report to Davy after his first trial, he wrote: "I had a strong desire to breath intoxicating gas, for two reasons. First that I might know the effects and sensations which this gas communicates. And secondly to see how far I would be able to guide myself by reason. On both these heads I was fully satisfied as this statement will show. When breathing this gas the first thing I felt was a dilating of the stomach and lungs; which was followed by a very pleasant sweet taste. A most delighting sensation then followed over the whole body, and particularly thro' the limbs. My head grew light and giddy, and I thought I was mounting thro' the heavens with ease and rapidity. At every respiration my speed seemed much accelerated. The longer I breathed the more I wished to breathe the gas; and with regret felt you pulling it from me. My lungs were then playing with uncommon quickness. During the whole process I felt much inclined to laugh, which burst forth when the pipe was pulled from my mouth . . . The idea of Lecturing then occurred and my pleasant sensations were all I felt inclined to relate, but was at a loss for words to convey them; for I found nothing in the world to which I could assimilate these feelings. The rapidity with which ideas glided thro' my mind was astonishing, and more than two-thirds of them one forgot. . . . I was sensible of all I did, but could not restrain myself, I knew some of the actions to be foolish, but they seemed pleasant, and I felt strongly inclined to perform them".

He paid a visit to London in May 1805, with an introduction from Lord Glasgow to Lord Dundas, the First Lord of the Admiralty, the friend and patron of Sir Humphry Davy, who introduced him to many prominent scientific contemporaries including his assistant, Michael Faraday, Brewster, Wollaston and Henry, with all of whom he remained in correspondence for most of his life.

Apart from the fact that his professorial duties seem to have been rather unduly heavy, little information concerning his life at this period is available, although we know from Sir William Hooker that he was a good linguist and a fair classical scholar. He was well acquainted with both English and foreign literature, and was deeply read in theology and Biblical criticism. On his annual visit to Lord Glasgow in 1807 he was encouraged to "bring and play his double flageolet as usual". He seems also to have been a fisherman, since amongst his papers is permission from the Duke of Argyll for him to fish his lochs and rivers at any time when his own family did not wish to do so; and he was presumably a skilful curler since he was made a member *honoris causa* of the Glasgow Club. He acted as Honorary Surgeon to the 7th Regiment of Scottish Militia (The Angus Fencibles) at the request of Lord Glasgow, and attended an "exercise" in 1804 in which the newest recruits, under the guise of a raiding French force, had to land and be driven off no less than three times by their more veteran colleagues who were provided with 50 "shotless cartridges" for this purpose. He mentions in one of his later letters that although he sympathized with the educational aspirations of the Radicals, his principles were (and remained) "soundly Conservative"! He also seems to have carried on a private medical consulting practice with some success as is testified by a letter from a patient thanking him for curing him of a terrible skin complaint at which no less than thirteen other medical gentlemen had previously tried their hand; although he does not seem ever to have attained to financial affluence. His patron Lord Glasgow started at this time the running correspondence with him regarding his own health, which he continued until his death in 1843; and sometimes when Ure went, *en famille*, to spend his annual holiday with him at Kelburn Castle, he would present him with fifty guineas on the pretence that he had taken him from his professional duties in Glasgow.

In 1804 he inaugurated his celebrated series of "Mechanics' Classes" in popular science and its industrial applications for working men, which were, according to the *Dictionary of National Biography* (*D.B.N.*) probably the first of their kind and which also became immensely popular; this was to "diffuse amongst the manufacturers and mechanics of Glasgow a knowledge of the scientific principles of their respective Arts". In 1807 he added a library by public subscription, giving several lectures for this purpose, and presenting 100 volumes of his own. In 1810 we find him in correspondence with Josiah Wedgwood, son of the great potter, who was making the porcelain parts of his electrical apparatus, but who seems not only to have been very slow in doing so but, in the view of the youthful professor, avaricious in his demands for payment!

Dr. Ure assisted notably during this period in the development of the Andersonian Institution, especially of its medical school (which, with his help, by 1828 had five professors and had acquired the premises of the old Grammar School). His laboratory in this building

is believed to have been the first in which class instruction in practical chemistry was given in Europe; a contemporary document describes him as "the chief ornament" of this Institution. He also filled the post of Lecturer in Materia Medica, probably in the Portland Road School, and in 1813 he published, under the auspices of the Faculty of Physicians and Surgeons, "A New Systematic Table of the *Materia Medica* with a Dissertation on the Operation of Medicines", which he claims to be the first work on scientific pharmacology.

In 1808 he again visited London, this time to discuss the project of establishing an observatory in Glasgow. He made the acquaintance of Nevil Maskelyne, Sir David Brewster, Groombridge, Troughton, Pond and others, with whom he also remained in constant correspondence throughout his life. The observatory was founded by him and others in the following year, and he was put in charge and resided in it for several years, leaving it second only to Greenwich in reputation at that time. Whilst in residence he was visited by Sir William Herschel, the Astronomer Royal, who gave some lectures to the local Astronomical Society and helped him to install a fourteen-foot reflecting telescope of his own design and manufacture. He was elected Fellow of the (Royal) Astronomical Society in 1811. Herschel's second son many years later (in 1866) came to occupy Dr. Ure's Chair in Natural Philosophy.

In October 1816 he paid a courtesy visit to Paris with his friend the 7th Lord Elgin (of the Elgin Marbles), at the invitation of the French Academy, transmitted through Marshal Berthier, shortly before he committed suicide. He met many leading scientists including Cuvier (with whom he visited the field of Waterloo and returned with an eagle trophy), Berzelius the Swede, Berthollet and his assistant Guy-Lussac; and since he wrote and spoke French well he was a considerable success. The next year his Institution was visited officially by Baron Charles Dupin on behalf of the French Government, who was particularly impressed by his Mechanics' Class. This led to the establishment of similar courses at the Ecole des Arts et Métiers in Paris. Baron Dupin stated in his official report to his Government that Dr. Ure "a produit des resultats étonnants. C'est une chose admirable que de voir aujourd'hui dans beaucoups d'ateliers de Glasgow de simples ouvriers poséder et développer au besoin les principes de leurs operations et les moyens théoretiques d'arriver aux resultats pratiques les plus parfaits possibles". Another report written the previous year states that "Europe affords no similar example of a class composed of several hundred artisans, mechanicians and engineers weekly assembled (8 p.m. on Saturdays) to study the scientific experiments . . . it is much to be desired that similar courses shall be instituted in all big towns of the British Empire". As the result of this, and other reports, Dr. Ure received visits from many of the most notable Continental scientists and became the recipient of many honorary diplomas from the chief scientific institutions of both Europe and America. It is recorded that the proprietors of the great factories in England, Scotland and Europe encouraged the attendance of their leading artisans by distributing tickets "for the most deserving" until about 1820 when the general schism between masters and men began to spread through the manufacturing districts, which resulted during the Industrial Revolution in the emergence of Disraeli's "two nations" and the mass employment of unskilled labour as machine-minders and so the disappearance of the skilled artisan.

In 1813 Ure was appointed Professor of Natural Philosophy and Chemistry at the Belfast Academical Institution, this seems, however, to have involved only a compulsory course of lectures every two years; his visits inaugurated his interest in the scientific aspect of bleaching and milling, however, about which he later wrote.

In 1817 he embarked upon an important series of researches connected with various subjects lying within the domains of both physics and chemistry, most of which can be found in the *Philosophical Transactions of the Royal Society*. Amongst these was an important series of determinations of the specific gravity of sulphuric acid in varying dilutions (*Journal of the Royal Institution*) which was a remarkable and early example of the useful application of logarithms to chemistry; and a paper on the latent heat of vapours which formed the basis of many modern meteorological theories. He also described an explosive eudiometer for gas analysis, which bears his name. On December 10, 1818, he read a paper to the Glasgow Literary Society on some pioneer experiments he had performed with the galvanic current on the body of Clydesdale, the murderer, and suggested that by early stimulation of the phrenic or vagus nerves or the great sympathetic in the neck, life might be restored after suffocation or drowning. These experiments caused a considerable sensation according to the *D.N.B.*, and found an echo in Byron's poem *Don Juan*. Some extracts from the published account of these experiments may be quoted. "The murderer was a middle-sized muscular man of 30. He was suspended on the gallows for nearly an hour, and the experiments were made in the anatomy theatre within ten minutes of him being cut down. There was no dislocation of the neck." Dr. Ure connected his galvanic rods firstly with the spinal marrow and the sciatic nerve through deep incisions, whereupon "every muscle of the body was immediately agitated with convulsive movements resembling a violent shuddering from cold. On moving the second rod from hip to heel the knee being previously bent, the leg was

thrown out with such violence as nearly to overturn one of the assistants, who in vain tried to prevent its extension". The body was also made to perform the movements of breathing, by stimulating the phrenic nerve and the diaphragm. "In the judgement of many scientific gentlemen who witnessed this scene, this respiratory experiment was perhaps the most striking ever made with a philosophical apparatus. . . . " Later "every muscle of his countenance was simultaneously thrown into fearful action, rage, anguish, horror, despair, and ghastly smiles united their hideous expression in the murderer's face, surpassing far the wildest representation of a Fuseli or a Kean. At this period several of the spectators were forced to leave the apartment from terror or sickness, and one gentleman fainted". One of Dr. Ure's chief contributions to the discussion which was then raging regarding the effect of the application of galvanic "animal electricity" to the body, was to point out what had previously been overlooked, namely "that a muscular mass through which the galvanic energy is directly transmitted exhibits very weak contraction in comparison with that which can be excited by passing the current through the principal nerve of the muscle".

In 1818 he was able to prepare a table of specific gravity for nitric acid in different dilutions, and he applied electricity to the problem of saline crystallization for the first time. He also published a very important paper on the relationship of chlorine to hydrochloric acid in the *Edinburgh Philosophical Transactions*. In 1821 he published his great *Dictionary of Chemistry* in two volumes; this also constituted a "System" of chemistry and rapidly passed through four editions and was translated into many languages including French (Riffault, 1821), German, Spanish and Russian. The American edition (1841, Philadelphia) became the standard textbook on the subject and remained so for many years. It contained some of the earliest accurate researches in organic chemistry, and led to his election to Fellowship of the Royal Society in the next year (1822). It was dedicated to his friend and patron the Earl of Glasgow "In gratitude for his favour at the onset of my life which cherished those studious pursuits which have since formed my chief pleasure and business", and also "for His Lordship's hospitality to which I owe the elegant retirement in which many of these pages were written".

About this time he was able to gratify his frequently expressed desire to visit Cambridge, "the most celebrated seminary of European science". He did so at the invitation of the Professor of Chemistry and spent a week giving demonstrations of his much admired experimental technique. Tribute to this is contained in a letter written to him after his departure by Professor E. D. Clark, in which he says "I wish very much you had examined the small quantity of gas which you collected from Plutonium. It remained on my table long after we lost you because the experiment required a hand like yours, and *we* could do nothing with it"! He also paid another visit to Paris where after exploring the catacombs he bought himself "four fancy waistcoats in satin and velour", and a turquoise ring for his daughter for which he paid 20 francs!

At the end of this year he expanded his researches into organic chemistry and published a long paper "On the ultimate analysis of vegetable and animal substances" in the *Philosophical Transactions*. Of this Dr. Beattie wrote poetically later " . . . 'T was his mysterious regions to explore, And scatter light where all was doubt before"! From this time onwards he also published by request, a succession of valuable chemical reports on foreign science, including methodical digests of literature with comments and comparisons with British science, in the *Quarterly Journal of Science*, of which his friend T. W. Brande, Secretary of the Royal Society, was Editor. This was perhaps the first recorded regular scientific abstracting service. His energy seems to have been enormous, for in addition to his books, no less than fifty-seven original papers are to be found in the *Philosophical Transactions* alone, covering many aspects of pure and applied chemistry, physics, optics, electricity and mechanics.

In 1821 his Mechanics' Class asked him to use a subscription they had raised to get Dr. Birkbeck's portrait painted by some eminent artist of his choosing, to hang in the Institute; at the same time he himself received "A chronometer of the best workmanship and a laudatory address". It was at the end of this year that he quarrelled with Dr. William Henry, the eminent chemist, whom he accused of plagiarism. Dr. Wollaston, a friend of both parties, was asked to arbitrate, but compromised by appointing a friend unknown to either of them to do so. His report, a model of tact, proved agreeable to them both and their friendship was later renewed. Later in this year he was also invited to visit the Royal Arsenal at Woolwich, with Major Henry Kator (later Treasurer of the Royal Society), to witness the practice firing of the rocket batteries which had been invented by the superintendent, Sir William Congreve, and to make suggestions for their improvement. These had been used at the battle of Leipzig in 1813 with disappointing results so far as the enemy were concerned, but the War Office, urged on personally by the King, were still at that time hoping to increase their future wartime value.

In 1824 he published the *Elements of the Art of Bleaching* (two volumes), which he translated

from the French of his friend Berthollet, receiving 200 guineas and a dozen copies as his reward. In 1829 "A New System of Geology" appeared, in which he pointed out the importance to this subject of chemistry and physics, and the fact that sacred history can be reconciled with its findings. It was one of the last textbooks in which the influence of Noah's flood was insisted upon. For this work he received 500 guineas and was elected an original member of the Geological Society. By means of this volume his poetic admirer states that "He harmonised Divine with human lore, and weighed *this* life with that which lies before"! Later in this year the City of Glasgow decided to erect a public monument to James Watt, the engineer, and at the request of the Lord Provost, Dr. Ure gave a public lecture at Christmas on the steam engine "illustrated by an elegant series of working models" to initiate the fund.

The Move to London

By 1829 he was finding it necessary to undertake the lengthy and expensive journey to London very frequently in order to supervise his various publications, and to attend the meetings of the Royal Society to which he was contributing greatly. He seems also to have obtained the unofficial offer of the Chair of Chemistry at University College, London, which was in the process of being founded by Lord Brougham, who as Lord Rector of Glasgow University and a great supporter of public education, knew and admired Dr. Ure's pioneer work in this field. It was probably this possibility which finally decided him to move his family to London, which he did in 1830. The professorship, however, went elsewhere, as the result, it seems, of unexpected opposition fermented by Dr. Thomas Thomson, F.R.S., the Regius Professor of Chemistry at Glasgow, whose "First principles of Chemistry" Dr. Ure had reviewed somewhat harshly in the *Quarterly Journal of Science*—"a more arrogant and truly mischievous publication.... The Regius Professor is taking Royal liberties with the labours and property of others"! In a private letter to Ure the Editor (Brande) wrote regarding another similar review "I have as usual blunted some of the shafts of your criticism . . . just though they are!"

After a few months in rooms in Howland and Keppel Streets, Bloomsbury, he took a house at 21, Finsbury Square, where he lived until 1834, when he moved to 13, Charlotte Street, Bedford Square, which was his home until about 1845 when he went to live with his son Alexander at 18, Upper Seymour Place, where he died.

His friend Brande, who as Editor of the *Quarterly Journal of Science and Art* was relying increasingly upon his collaboration, secured him the post of Lecturer in Chemistry to the Surrey Institution, and later to the Royal Institution, where he had succeeded Sir Humphry Davy as Professor of Chemistry, and the Apothecaries' Hall. From correspondence at this period between Brande, John Murray the publisher, and Dr. Ure, it is interesting to learn that Murray, in spite of his great reputation, had his faults. Brande says "Murray is terribly negligent but means no offence by what in others would appear impertinent negligence" (December 11); and again "Mr. Murray is not the man of business a bookseller should be, though he has many advantages etc." (March 20): whilst Ure, in spite of his meticulously accurate outlook on science, seems always to have sent his manuscripts just too late to allow of him correcting the proofs, a bone of contention with Brande which recurs through the years.

Dr. Ure set up in 1830 in private practice as a consultant in science in all its branches, and more particularly as an analytical chemist for commercial purposes. It was said of him by Sir Michael Faraday, after his death, that "his skill and accuracy were well known as well as the ingenuity of the methods employed in his researches . . . and it has been stated that no one of his results has ever been impugned. His extensive knowledge enabled him to arrive at conclusions, and to demonstrate facts considered impossible by his compeers in science". Some idea of the variety of his practice and "the amazing and varied fund of knowledge of applied science on which he was consulted from all over the world" (*British Medical Journal*) can be gained from the following brief list which has been culled from his letters or publications: The disinfecting of ships and their cargoes (Lord Lansdowne), bread-baking processes, distilling, a new process of amalgamating zinc and copper, analysis of a metal tool and an ointment found by Sir Gardiner Wilkinson in an Egyptian tomb, infringement of a patent concerned in piano construction (Messrs. Broadwood), several photographic patents of his own, and the analysis of various types of coal for the Admiralty. He also visited professionally most of the new Midland industrial areas, and some in France and Belgium, to advise upon technical improvements, chiefly in cotton manufacture, bleaching and dying processes, glass manufacture, and mining; many of the leading industrialists being old pupils of his. In 1833 he was requested by the Lords of the Committee of the Privy Council to undertake experimental researches into sugar refining, and his report was printed by order of the House of Commons, and led to the fixation of the sugar duties. He also undertook for them the investigation of methods of estimating the amount of sugar in sugar-cane juice, for which he was paid £800. In the following year he was appointed first

consulting analytical chemist to the Board of Customs, a post which he held until his death.

He seems to have enjoyed the scientific and social life of London; his "Sunday Savants' breakfasts" and his "5.30 beefsteak parties" appear to have been popular and frequented by most of the notabilities of the time including Lord Glasgow who had taken a town house in the same neighbourhood. At these he employed to the full his exceptional mental energy and powers of conversation, and always proudly displayed the silver teapot presented to him by his Mechanics' Class in 1809. His daughter Mrs. Mackinlay continued later to preside over a weekly "salon" in Soho Square until nearly the end of the century.

In 1835 he brought out the fourth edition of his *Dictionary of Chemistry*, as well as *Philosophy of Manufactures* which went into several English editions and was translated into French and German. In this is perhaps to be found the beginnings of social medicine, since he deals from a medical aspect with the conditions of the workers in the cotton mills, and advocates special methods of ventilation and heating. These views were expanded next year (1836) into *The Cotton Manufactures of Great Britain—Scientifically Investigated and Compared with that of Other Countries* (two volumes). His friend James Nasmyth, the great engineer, executed most of the 1,240 fine drawings with which this work is embellished. Having focused interest on the subject of artificial ventilation in buildings, he was asked to design a system to be installed in the new Customs House of the Port of London, and later for the Reform Club. He was consulted also regarding the heating and ventilation of the new Houses of Parliament but his suggestions, to his great annoyance, were not carried out. He undertook at this time also an extensive series of soil and mineral analyses for Lord Breadalbane on his estates, and was appointed scientific member of a "Metal and Paint Commission" set up by the Army under the Chairmanship of the Commanding Royal Engineer. He explored the original idea that sugar might be obtained in commercial quantities from beet, and carried out several analyses of the amount actually contained in root-syrup of varying origins. Characteristically he wrote an equally lengthy exposé of a popular moustache cream which he had been requested to analyse! His printed tariff of charges for his investigations is of some interest:

Dr. Ure's ordinary Fees or Charges for Chemical Analysis, or for business relative to the application of Science to the Arts and Manufactures, are as follows, viz.:

	£	s.	d.
For consultation respecting any single point or question of inquiry	1	1	0
Written opinion upon a short case, or letter of inquiry	2	2	0
For a series of chemical experiments (unless by special agreement) per day ...	5	5	0
Examination of any soil, earth, metallic ore, or other mineral, simply to ascertain its chemical nature	3	3	0
Complete analysis of ditto	10	10	0
Report on the nature of any mineral water	2	2	0
Complete analysis of ditto	10	10	0
Attendance in London to view any manufactory; to examine apparatus; or to inspect any chemical process; for the purpose of suggesting improvements, or of preparing evidence, or of instructing counsel, &c., and reporting thereon	4	4	0
For similar attendance which shall occupy the whole or the chief part of the day	6	6	0
Attendance at a distance from London, exclusive of travelling or other actual expenses, per day...	7	7	0

In 1837 his chief and most encylopædic work was published, the great *Dictionary of Arts, Manufactures and Mines* (two volumes) for which he received 1,000 guineas and twenty copies from Messrs. Longmans, Green & Co. (He twice left his green calico umbrella in Mr. Longman's office.) Further enlarged editions were rapidly called for in 1840, 1843 and 1853. After his death four further editions appeared, the last in 1878. This work was translated into almost every European language, including Russian and Spanish; as *The Times* review of it said: "This is a book of vast research, and the variety of subjects embraced in it may be estimated by the fact that on the French translation it was thought advisable to employ nineteen collaborators, all regarded as experts in their special subjects. Dr. Ure thus honourably occupies a position in scientific work analogous to the literary feat of Dr. Johnson, who single-handed produced his *English Dictionary*."

In 1842 he was successful in obtaining damages in the High Court for a client living in 11, George Street, Hanover Square, who stated that his front rooms had been darkened by the erection of a hoarding. By practical demonstration with a method of photometry devised by himself, he convinced the Judge and jury that 15% of his client's light had been filched! During this year he was also engaged in some crucial experiments on the polarization of light at the request of his friend Sir David Brewster.

As his purely scientific work increased he seems to have relinquished the practice of medicine, although his correspondence shows him to have remained upon the best of terms socially with leaders of the profession such as Sir Henry Halford, Dr. R. H. Hume, and Dr. J. A. Paris, the President of the Royal College of Physicians.

In 1844 he summarized the chemical processes involved in bleaching, together with his own not inconsiderable contributions to the industry, in a book entitled *Chemistry Simplified in its Application to the Testing of Alkalis, Acids and Bleaching Substances*. He also attacked white bread and the processes used to obtain it, and pleaded for the establishment of a *Board*

of Health to be composed of eminent physicians, chemists and engineers, to watch over markets, factories, bakeries, abattoirs, places of public amusement and secret medicines. A year or two later, when passing through Rouen with his daughter, the Mayor invited him officially to inspect the local factories. According to a letter written later by her, when they reached the gates of the largest factory they found the approaches lined with a hundred cheering artisans, who had in the past attended his Mechanics' Classes in Glasgow. Many of these had subsequently achieved important and responsible positions, and paid public tribute to his enlightened ideas and lucid teaching.

In 1850 he was asked by the Commissioners of Metropolitan Sewers to investigate independently what was known as the Pimlico Malaria tragedy, in which several sewermen and others had lost their lives. An official report by four distinguished chemical scientists had recently whitewashed the authorities, but the public, especially *The Times*, were not satisfied. His long printed report is entitled *The General Malaria of London and the Peculiar Malaria of Pimlico, Investigated, and the Means of Their Economical Removal Ascertained.* In this he proves that no natural disease processes were involved, but that the deaths were due to the poisonous exhalations of cyanogen compounds produced by chemical action from refuse dumped there. He is rather unkind in his comments on the official report and its scientific compilers, and he proposes for the purpose of such future investigations the formation of an impartial Science Tribunal "which shall not swarm like our present Royal Society with vain dilettanti having the form of philosophers, but strangers to their powers and methods of research". He also suggested the possibility of smoke prevention in factories, and predicted that this would increase public health.

Last Years

During his last years, although he retained to the end his mental clarity and love of good conversation, his activities were much limited by what was termed gout of his right side, thigh and leg, after any physical exertion. He had mentioned this in his letters from 1829 onwards, and had visited many Continental spas with his devoted daughter, where he combined his treatment with analyses of the waters; these were still quoted until the recent war in some smaller German resorts. He also for several years abstained from all butcher's meat and wine, without relief, and in 1841 he wrote that he proposed to visit Dieppe where he would join his old friends M. Clement (the Professor of Chemistry in Paris) and Baron Cuvier, the naturalist, in a "cure" by means of sea-bathing at the Royal Baths there. Possibly the modern diagnosis would substitute an intervertebral disc lesion for gout?

To conclude, in the words of Duncan's *Memorials*: "These various labours in widely differing fields show the great versatility of the man, whilst his publications were largely responsible for the interest shown by his contemporaries in other walks of life in popular science." He was a deeply religious man and was held in affection by a wide circle of friends which included the poet William Beattie, whose funeral Ode, which was published in *The Times*, stated: "The last sad office to our friend is paid, Affection lingers where his dust is laid." Some years later a memorial tablet was erected to his memory in Glasgow Cathedral, where it may still be seen.

Several portraits of Dr. Ure survive, two by Sir Daniel McNee, P.R.S.A., one of which is in the Victoria and Albert Museum, and a rather charming water-colour sketch as a young man which is in the National Portrait Gallery. (*See* page 656.)

My grateful thanks are due for considerable help received from Dr. Ashworth Underwood, Director of the Wellcome Historical Museum, Dr. J. J. Keevil, Librarian of the Royal College of Physicians, and Mr. George Thompson of the Royal Glasgow Technical College.

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Section of Radiology

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Isotope Research and Clinical Radiology

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CLINICAL radiology only a few years ago was confined to X-ray diagnosis and to X-ray and radium—chiefly gamma ray—therapy. Discovery of artificial radioactivity made available a new radiological tool for investigation, diagnosis and treatment of disease. Since 1935 various radio-isotopes have been used increasingly in the study of biological processes. By using the appropriate isotope it was shown that this method of investigation, in some ways better than classical chemistry, serves to shed light on the nature of physiological and pathological processes. Chemical analysis used as a clinical laboratory method provides qualitative and quantitative information about a condition at any given moment. Biochemical procedures do not provide information about the dynamics of digestion, assimilation and excretion, nor do they permit determination of the particular fraction of an end-product which results from material ingested two days previously, as compared with that which is present in the tissues from an earlier or later ingestion. The administration of elements which are physiological constituents in radioactive form overcomes these limitations of classical chemistry in elucidating processes of metabolism.

Radio-isotopes differ from stable atoms only in having radioactive properties, and in the slight difference of atomic weight. Biological effects are due apparently to the radiation emitted in the course of disintegration of the radioactive atom. The biological effects depend on the quality and quantity of radiation. Qualitative differences are due to the specific ionization more than to the energy of emitted particles or photons. Alpha particles produce very dense ionization and have biological effects some ten times greater than gamma rays of the same energy. Beta particles are absorbed in a few millimetres of tissue, while gamma rays of equal energy penetrate several hundred times that thickness. The effects of varying quantities of radiation are dependent on the tissues and on the amount of energy absorbed in a particular tissue. Qualitative and quantitative effects of radiations from radio-isotopes of course constitute a limiting factor in their use in the study of living organisms.

By means of radio-isotopes clinical radiology may expand into the field of clinical laboratory procedures. Roentgenology of the past has been a method of macroscopic morphology. Artificial radioactivity provides the means of demonstrating microscopic morphology by localizing the constituents of tissues, cell aggregates, and single cells, thus directing radiology into the field of cytology. By introducing a method of studying the time factor in morphological changes, radioactive isotopes may bring radiology into the realm of cell physiology as well.

During the last fifteen years radio-isotopes have been used extensively to pursue three general lines of investigation: (1) the distribution of active and passive metabolites in the body; (2) investigation of some of the mechanisms of metabolism; (3) investigation of the therapeutic applicability of artificial radioactive isotopes.

Distribution Studies

Some of the many studies of distribution of radio-isotopes serve to illustrate the possibilities of the first line of investigation. Time does not permit of more than a brief sketch of those which have greatest significance for clinical radiology.

Phosphorus, which is a universal cell metabolite, is particularly suitable for studying distribution patterns within the body. A number of such studies have established that initial uptake of phosphorus is highest in liver, spleen, kidneys and bone-marrow. The longer the time interval between administration of P^{32} and observation of uptake, the greater the concentration in the skeleton. Parenthetically, studies have shown that turnover of P^{32} is higher by at least four times in growing epiphysis than in shaft. Tissues which metabolize slowly, on the other hand, such as fat, cartilage, and brain, show relatively lowest concentration of P^{32}, and a differential concentration of P^{32} within the brain has been demonstrated, wherein the pineal body, the pituitary, and the hypothalamus concentrate most of the P^{32} which is taken up by the brain. Within cell aggregates such as leucocytes, it has been shown that almost all the P^{32} which is concentrated by the cells appears during the first forty-eight hours in the acid soluble fraction. After forty-eight hours increasing amounts of P^{32} are found in the nucleoprotein and phospholipid fractions, suggesting that enzymatic carrier systems are active in the transfer of phosphorus from acid soluble to nucleoprotein and phospholipid fractions. Studies of leukæmic blood, moreover, have shown that in myelocytes the nuclei concentrate appreciably more P^{32} than the cytoplasm, while in lymphocytes, concentration of P^{32} in nucleus and cytoplasm is about equal.

Certain studies of phosphorus distribution have been concerned with uptake in localized neoplastic tissue, as compared with normal tissue in the same subject. These investigations have illustrated clearly the preferential uptake of phosphorus by leukæmic and neoplastic tissues. The amount of uptake and the retention are dependent on the total phosphorus content of the tissues, on the rate of turnover within the tissue, and on the rate of growth of new tissue. The relatively high uptake of P^{32} by certain brain tumours has been utilized in localizing such tumours *during* surgery by means of probe counters inserted into the tissues.

The selective uptake of phosphorus by many tumours has been exploited in the pre-operative diagnosis of such tumours by *surface measurements* where counts taken over the lesion and over comparable uninvolved tissue show differential concentration of radio-phosphorus. In order to be investigated in this manner, lesions must of course be situated superficially—not more than 5 mm. beneath the surface of the skin. Many breast tumours and testicular tumours are so situated, and so are most suitable for diagnosis by surface measurement. The method has proved accurate in 89% of malignant tumours of the breast, 91% of benign tumours of the breast, 100% of inflammations, and 100% of seminomas. It is not suggested that the method be used to obviate surgical exploration. However, it is certainly of assistance to the surgeon to know in advance what sort of lesion he will encounter and whether the condition is complicated by the presence of inflammation. In addition, the method has the great advantage of permitting repeated examinations in order to follow the effect of a course of therapy such as hormone treatment, or radiation. Diminished concentration of P^{32} in the lesion indicates less active growth of tumour tissue.

The principle of surface measurement is useful also in localizing brain tumours pre-operatively. In this procedure I^{131} is linked to fluorescein to make the diiodofluorescein molecule which is selectively concentrated by brain tumour tissue. Measurements are made over the skull at various points.

Phosphorus, because of its ability to permeate red blood cells, has been used to measure circulating red blood cell volume. The procedure of labelling erythrocytes has been carried out with a number of different isotopes, including iron, and appears to be a more accurate method of blood volume determination than either dye or hæmatocrit methods.

Sodium, which is chiefly an extracellular metabolite, provides a more accurate method of measuring extracellular fluid volume than either sucrose, sulphate, or thiocyanate. This method gives values of about 21% of body-weight as sodium space, of which 15% is plasma and 85% interstitial fluid.

The observation that the concentration of radiosodium in pleural and ascitic fluids is essentially the same as in blood serum affords a useful means of estimating the volume of excess extracellular fluid in patients, by comparing sodium space values for such patients with values for normal subjects of equal body-weight.

Radiosodium has been used successfully in the localization of placenta. Counts made over the abdomen following a dose of Na^{24} will indicate the position of the placenta. The procedure may become important in the localization of placenta prævia.

A major subject of distribution study has been the concentration of iodine by the thyroid gland. It was early established by largely qualitative methods that thyroid concentrates iodine in accordance with its degree of function and hence of its need for this metabolite. Normal subjects were shown to reach highest uptake approximately two days after administration of a test dose. Patients with non-toxic goitre and normal B.M.R. showed uptake 10 to 12% higher than normal subjects. Patients with thyrotoxicosis showed highest uptake about one to four hours after administration of radioiodine, and they showed a rapid decrease in radioiodine content so that two days after administration often only about 5% of the administered dose remained in the gland. Patients with hypothyroidism without goitre showed exceedingly low uptake and exhibited curves without any true peak. In thyroiditis uptake was very low, and in hyperplastic tissue uptake was higher than in involuted tissue.

For the most part patients with thyroid carcinoma show very low uptake. Histological studies of thyroids of a group of such patients compared with radio-autographs demonstrated that structure of the tumour tissue is a determining factor in the ability to collect radioiodine. Orderly cell arrangement in follicular pattern and presence of colloid material are essential to radioiodine uptake in both primary and metastatic tumours. It has been shown that during the first three days after administration radioiodine is concentrated in the cells and subsequently it is found in the colloid. Much thyroid tumour tissue, however, is heterogeneous in structure and this accounts for non-uniform uptake in many thyroid tumours. Accordingly a single biopsy cannot be relied upon as being representative of radioiodine uptake throughout the tumour.

It was hoped that differences in capacity of thyroid tissue to concentrate radioiodine would constitute a possible means of establishing differential diagnosis of thyroid disease. In practice, however, experience has shown that there are no clear-cut patterns of uptake and retention, and overlapping has been observed between groups of euthyroid subjects and patients with thyrotoxicosis on the one hand, and between euthyroid subjects and patients with myxœdema on the other.

While the distribution of a metabolite isotope as determined by uptake study is of great significance for determining the avidity of certain tissues and organs for the metabolite, such findings in most instances do not reveal anything about the mechanism of organ or tissue function.

These considerations have especially important bearing on our second general topic of discussion, namely, investigations of the mechanism of metabolism and organ function by means of radio-active isotopes.

Investigation of Mechanism of Metabolism and Organ Function

Radiophosphorus has been used to study phospholipid metabolism. Animal experiments have established the rate of turnover of phosphatides and have shown that the synthesis of phospholipids is primarily a function of the liver. Plasma phospholipid concentration is thus a measure of liver function in this regard. Test doses of radiophosphorus have been administered to patients with hyperlipæmia and the rate of appearance of phospholipid in the plasma has been determined. It was found that, irrespective of the cause of hyperlipæmia, a high phospholipid plasma level indicated overproduction of phospholipid by the liver rather than accumulation due to biliary obstruction or to decreased breakdown of the phospholipid molecules by the tissues. The effect of choline and methionine on phospholipid production has also been studied in patients with cirrhosis of the liver. P^{32} administered intramuscularly was used as an indicator. It was observed that a single large dose of either choline or methionine produced an increase in the rate of turnover of phospholipid in these patients. No such increase in turnover rate occurred after protracted administration of methionine, or after administration of a single large dose of choline following protracted treatment with methionine. This suggests that increased turnover following a single large dose of either choline or methionine reflects a relative deficiency of lipotropic agents. The degree of response is probably an indication of the value to be anticipated from treatment of cirrhosis with lipotropic agents. It seems worth while pointing out the fact that isotope technique has contributed knowledge of a significant character to the intricate problem of liver function.

Administration of radiosodium to human subjects in shock from severe burns shows increased sodium space without commensurate increase in body fluid, and at the same time there is a disappearance of sodium from the urine. Such observations suggest that the anti-sodium barrier between intracellular and extracellular fluids has been affected and that sodium is infiltrating tissues where it does not normally go. Thus certain parts of the body are deprived of their normal sodium supply. Based on this knowledge it has been found that

treatment of patients suffering from severe burns with sodium lactate solution is remedial. Apparently administration of sodium in this form by infusion or orally serves to re-establish fluid balances and to maintain blood volume and blood pressure.

Radioiron has also been used in studies of shock to measure stagnation of blood cells. Widespread stagnation of red cells was demonstrated by the radio-isotope method, and was related by the investigators to mean arterial pressure since it had been shown to be independent of blood loss. This in turn suggested the desirability of introducing red cells in transfusions as well as plasma, in order to avoid starvation of parenchymal cells due to stagnation.

I have referred earlier to the general patterns of uptake of radioiodine by the thyroid gland. The clinical usefulness of these observations, however, depends upon linking the utilization of iodine to thyroid function, and for this, more complete investigation of the dynamics of iodine metabolism is needed. Radioiodine has two uses in clinical radiology—one as a means of delivering therapeutic amounts of radiation to the thyroid, and second as a means of distinguishing among various disorders of thyroid function. Early efforts to use radio iodine as a diagnostic tool were somewhat disappointing due to two fallacies, namely, that thyroid function could be determined by a simple measurement of degree and rapidity of uptake of radioiodine by the thyroid gland, and that biological material might be counted on to behave in a wholly consistent and homogeneous manner. That the second idea is a misconception is clearly demonstrated by the considerable overlapping in uptake values which occurs between euthyroid and thyrotoxicosis and myxœdema groups.

Refinement of technique has shown how much more can be learned concerning thyroid function than was possible by gross measurement of uptake at arbitrarily fixed intervals, together with determination of radioiodine excreted over the same period.

Although the percentage hourly uptake, the half-peak uptake, and the maximum uptake are valuable indicators of the avidity of the thyroid gland for iodine, no one of these values alone reflects the physiology of the gland which is a time-related function. It is obvious therefore that in every case the entire process of concentration and release of iodine must be known. There is unfortunately no short cut to the attainment of this knowledge. The function of the thyroid gland is the production of thyroxine which is released into the circulation as protein bound iodine. Thus the determination of protein bound radioiodine in the plasma is an essential clue to thyroid function. The total radioiodine plasma level is a measure of inorganic and protein bound iodine and so is not definitive concerning thyroid function. Similarly, a high clearance rate of radioiodine from the plasma together with normal excretion is an indication of thyroid avidity for iodine, but only subsequent determination of protein bound iodine will demonstrate the ability of the thyroid to convert the inorganic iodine, which it has collected, into thyroxine.

These considerations make clear the fact that the more facets of investigation are used, and the more the concept of a dynamic flux is kept in mind, the more nearly we shall succeed in narrowing the margin of error which exists in attempting to distinguish among various thyroid disorders by means of radioiodine. Nevertheless, we shall always find that the unavoidable variability of biological material tends at times to confuse the issue and to cloud certain of our results. For this reason it seems wiser to regard radioiodine as one very valuable tool for the investigation of thyroid disease which, when combined with protein-bound iodine determinations, B.M.R. studies, galactose-tolerance tests and other standard procedures, may serve to bring even borderline cases into the focus of correct diagnosis.

Therapy

Radio-isotopes are tools for the treatment of certain pathological conditions. Applied topically they constitute easily controlled sources of radiation, similar in effect to X-rays and radium. As internally administered agents their therapeutic effect depends on the biochemical role of the element or compound which contains radioactive atoms. Tissues, organs and organ systems concentrate metabolites selectively in accordance with their requirements and irrespective of the radioactive properties of the metabolite, so that a therapeutic effect can be attained if a tissue is capable of concentrating a particular radioisotope in adequate amount to deliver the desired dose of radiation. This fact, while it opens the way to employing a number of metabolites in radioactive form as therapeutic agents, at the same time accounts for certain limitations in the use of these materials.

The primary objective of all radiation therapy is the destruction of pathological tissue and the preservation of surrounding healthy tissue. It will be readily appreciated that the margin between the requirements of diseased and normal tissue for a certain radiometabolite may be too narrow to permit of a radiation dose sufficient to destroy the pathological tissue without undue damage to normal tissue. A case in point is the high uptake of strontium by both

normal bone and osteogenic sarcoma. It is not possible to avoid radiation damage to bone and bone-marrow when it is attempted to destroy osteogenic sarcoma by means of radio-strontium. In the case of more ubiquitous metabolites such as phosphorus and sodium, one must have in mind the effect on the whole body of administering therapeutic amounts of these substances in radioactive form.

Again because of their biochemical role, radio-isotopes remain in the body for varying lengths of time, and of course they continue to deliver radiation until they are eliminated or until their radiological decay is complete. In this respect they differ from external or topical irradiation in which the ionizing action continues only as long as the radiation source is applied.

Nevertheless, radio-isotopes are substantiating in increasing measure the early hope entertained for them. With improving knowledge of biochemical processes and of the biological effects of radiation, some of the radio-isotopes are being applied more effectively to certain pathological conditions. In a few instances they seem to offer better results than any other therapy.

As in any method of treatment, however, there are contra-indications as well as indications for the use of radioactive isotopes. In topical use where they either replace or act as adjuncts to X-rays and radium, no question arises concerning their applicability. For systemic use the radio-isotope must be judged for suitability by its physical and biochemical properties in relation to the pathological condition to be treated. In addition consideration must be given to the unavoidable exposure of healthy tissue to radiation and the immediate danger of untoward effect upon such tissue; and more especially one must keep in mind the possibility of late radiation damage.

Beta or gamma radiation from isotopes is utilized in topical application. Topical use includes surface application to the skin, implantation into tissues, infiltration of tissues, and intracavitary administration.

The effect of beta radiation on the skin has long been known. Beta particles have a finite range directly related to their energy, and they can penetrate skin to a depth of a few millimetres or even centimetres. Before the discovery of artificial radioactivity the sources of beta radiation were natural radioactive substances and cathode ray tubes. Neither of these sources provides pure beta or electron radiation. Many artificially radioactive substances provide pure beta radiation. Beta radiation from P^{32} has been shown to produce varying degrees of erythema, dependent on exposure. Based on this observation a technique has been developed for the treatment of such superficial skin lesions as basal-cell and squamous-cell carcinoma, hyperkeratosis, and hæmangioma by local application of P^{32}. Radioactive disodium-acid-phosphate of known activity is soaked into blotting paper discs of known dimensions, and dried. These discs can then be applied over any surface of the skin, held in place by adhesive tape, and kept in place for a period calculated to deliver the desired radiation dose. Exposure time is calculated in microcurie hours per square centimetre or surface rep. Calculations and measurements have shown that one microcurie per hour per square centimetre dissipates energy equivalent to approximately five rep. in the first millimetre of tissue. Measurements have also shown that 49% of the total radiation from a P^{32} plaque is absorbed in the first millimetre of tissue and the absorption is practically exponential.

While from the physical point of view the planimetric dose estimation may be correct, from the biological point of view, estimation of the total accrued energy in the tissue mass as a whole is more representative because it has been shown that the acute reaction of tissues is both sharply confined and uniform to a depth of 5 mm.

This method of treatment has resulted in destruction of superficial basal-cell and squamous-cell carcinomas in 94% of cases treated. It is particularly effective on curved surfaces where a homogeneous distribution of X-rays is impossible. It is valuable also in the treatment of hæmangiomas of the "strawberry type". It is not considered advisable for "port-wine type" hæmangiomas, or for deep-seated cavernous angiomas.

Strontium 89 is a beta radiator with similar radiation characteristics to P^{32}, and has proven of value in the treatment of superficial skin and ocular lesions.

A number of localized neoplasms amenable to intracavitary and interstitial irradiation with radium and radon have recently been treated with various radio-isotopes.

The isotope which seems in many ways to be the most promising for intracavitary and interstitial irradiation is radiocobalt.

The radioactive properties of radiocobalt make it a highly suitable source of external and interstitial radiation. It may be said to have as its only disadvantage a shorter half-life than radium, but it offers the following important advantages: (1) it emits low energy beta radiation—which can be screened easily—80 mg. per square centimetre silver stops beta radiation from Co entirely; (2) the gamma radiation is almost homogeneous—1·1 and 1·3 Mev.

photons are emitted; (3) no contamination occurs due to gaseous daughter-products; (4) there is rapid elimination of any Co which might enter the body; (5) Co is available in any desired quantities at a cost far below that of radium; (6) Co can be prepared in any shape and form and can be electroplated on any material and activated subsequently for clinical use; (7) Co is readily soluble and so may be used in solution in thin-walled containers for intracavitary use.

Flexible radiocobalt wire in nylon threads, and radiocobalt needles have been used successfully for interstitial radiation therapy. Recently dose calculation tables similar to the Paterson-Parker radium dosage tables have been prepared.

Radiocobalt beads have been used for intracavitary irradiation at the University of California for malignancies of the maxillary sinus, nasopharynx, urinary bladder, and uterine body cavity. Beads of 3 and 5 mm. diameter were activated to strengths of 0·6 to 6·0 millicuries for small beads, and 10 to 200 millicuries for larger beads. The beads were silver-plated to a thickness of 80 to 130 mg. per square centimetre. The beads were calibrated by the United States Bureau of Standards in roentgens per hour at 1 cm. Beads were used in preference to needles in order to approach more closely point sources of radiation. A Foley or Foley-Alcock catheter is used to hold the bead which is placed in the central channel in such a way that when the Foley bag is inflated the bead is in its centre. In this manner equidistant distribution of radiation is ensured. A deflated Foley bag is inserted into the cavity to be treated. The catheter is then inflated with an iodide solution. From the amount of fluid required to inflate the catheter the distance between the cobalt bead and the cavity wall can be determined and the radiation dose calculated. The dose is expressed in gamma roentgens at the wall of the cavity and at various depths. The dose is approximately radially uniform on all surfaces. Dose determination is based on phantom measurements and calculation of absorption in matter of electron density of soft tissues.

Doses of 6,000 to 8,000 r in five days have been tolerated without untoward reaction in cases of maxillary sinus and nasopharyngeal tumours. Tumour doses of 5,000 to 7,000 r in four to five days, and repeated after four weeks, have been well tolerated both in the acute post-radiation phase and during the three-year observation period, in tumours of the bladder. The radiocobalt method appears to be superior to any other form of radiation therapy for treatment of bladder tumours. It is also preferable to fulgurization of multiple papillomata of the bladder. The effectiveness of this method in uterine body tumour is still undetermined.

In general the effect of radiocobalt on tumour and surrounding tissue is comparable to that of radium.

The use of radiocobalt at a distance for telecobalt therapy has been suggested, but any advantage of this method over a one or two Mev. X-ray radiation-beam-unit appears to be questionable.

Radiosodium and radiocobalt in solution have been used in special Foley catheter-like balloons for irradiation of bladder tumours. Clinical results are promising, but the method is beset by problems which tend to restrict the usefulness of this technique. The effect of high energy beta radiation from Na^{24}, the complex problem of dosage calculation, and the mechanical problems of dealing with an isotope in liquid form in this procedure, all constitute limitations of the method.

The radio-isotope of zinc, Zn^{65}, has a half-life of 250 days. It has been shown that zinc is taken up rapidly by the liver and spleen and is rapidly lost from these organs. Radiozinc in colloidal form when infused intraperitoneally is known to remain in the peritoneum without diffusion for several hours. Based on these facts, radiozinc has been used experimentally in the treatment of advanced ovarian carcinoma. In some cases marked improvement and loss of ascites has followed this treatment. Similar results have been reported for the treatment of liver metastases of melanosarcoma with colloidal radioactive chromic phosphate. Radiogold has also been used in the treatment of inoperable ovarian malignancies, by tumour infusion, and improvement of the patients has resulted. The danger of this type of therapy is due to the large volume of tissue which is irradiated locally. The possibilities of local necrosis due to beta radiation, and in the case of radiozinc, the total body effect of gamma radiation, dictate a very conservative course in this type of therapy. The case for infiltration of tumours with radiogold is not well founded moreover, because the same treatment can be carried out with X-rays or radium, both of which permit more accurate calculation of dosage.

Only three radio-isotopes have so far proved their value in *systemic* radiation therapy. These are radiophosphorus and radioiodine, and to a lesser extent, radiosodium.

The use of P^{32} in chronic granulocytic and chronic lymphoid leukæmia and in polycythæmia vera is based on experimental findings that P^{32} in sufficient quantity has a depressing effect on hæmatopoiesis, and that phosphorus is selectively concentrated by bone, bone-marrow, leukæmic and neoplastic tissues.

Radiophosphorus in the form of isotonic disodium-acid-phosphate administered intravenously is well tolerated. Oral administration is less satisfactory because of interference

with absorption by processes of ingestion, the higher rate of excretion, and the difficulty in relating the dose administered to the dose retained.

In chronic granulocytic leukæmia a hæmatological remission is frequently produced with radiophosphorus and this may last several months or as much as a year. In doses of 0·5 to 2·0 millicuries, P^{32} does not cause radiation sickness. With larger doses, however, radiation sickness does occur. Splenomegaly, hepatomegaly, and lymphadenopathy decrease gradually under P^{32} therapy during early stages of the disease and they may disappear entirely within about four weeks of instituting treatment. In later stages of the disease the response is less satisfactory. In the terminal stage, P^{32} is just as ineffective as any other radiation therapy and impairs rather than benefits the patient's general condition.

In chronic lymphoid leukæmia the response to P^{32} is, in general, similar to that in chronic granulocytic leukæmia. Complete remissions are less frequently seen in chronic lymphoid leukæmia, and remissions which do occur are of shorter duration for the most part.

A certain lack of agreement exists with regard to the extent to which treatment of chronic leukæmia should be carried. Some clinicians believe that when the white blood cell count is brought down to about 50,000 no further treatment should be given until exacerbation of the disease process becomes evident through increased white cell count, enlargement of liver, spleen and glands. A more reasonable approach would seem to be to continue treatment in the first instance until the blood count is brought as near normal as possible. Erythropoiesis is of paramount importance in determining extent of treatment and the presence of pathological white cells in the peripheral circulation is of greater significance as a criterion of remission than the total leucocyte count. A complete remission in leukæmia is attained when the diagnosis cannot be made from the blood count or smears. It is not always possible, of course, to attain a complete remission. In cases of long duration especially, it is observed that attempts to bring the white cell and differential counts within normal limits are accompanied by depression of erythropoiesis. In such cases one must be satisfied with a partial remission. When a relapse occurs after remission, treatment is re-instituted, with the intent of bringing about another remission. An increase of total white cell count by more than 15,000, together with increase of primitive cells in peripheral blood, and increase in size of liver and spleen, are considered indications for resuming treatment. Increase of B.M.R. may precede these clinical manifestations by several weeks; its determination is therefore of great value in evaluating a particular case.

Certain investigators take the stand that radioresistance develops characteristically in leukæmia and in related disorders, due to radiation therapy. It is true that larger doses of radiation and more frequent treatment become necessary as the disease progresses. Finally even large doses of radiation fail to stem the progress of the pathological process. The gradual increase of primitive cells in bone-marrow and peripheral circulation, the progressive displacement of erythropoietic and megakaryocytic elements, and the natural history of the disease in treated and untreated cases, suggest very strongly the probability that increasing activity of the malignancy and not "radioresistance" is the cause of lessened response to radiation therapy. The complete lack of response in acute leukæmia would seem to substantiate this view.

Radiophosphorus has been completely unavailing in the treatment of any type of acute leukæmia.

In chronic leukæmias hæmatological response can be produced with single doses of from 2·0 to 6·0 millicuries of P^{32}. Experience has shown, however, that a closer control of dosage can be exercised by the administration of small doses of 0·5 to 1·5 millicuries at frequent intervals. In this way a radiation level appropriate to the condition can be maintained. Several patterns of fractionation are now in general use in the treatment of chronic leukæmia. These are (1) *Simple saturation* method consisting of one 2 to 3 millicurie dose followed by small doses to adjust the radiation level for excretion and decay; (2) *fractional saturation method* wherein an initial small fraction is followed by similar fractions every second or third day until the desired radiation level is attained. This level may then be maintained by additional fractions. Usually the initial dose is 500 microcuries, and subsequent fractions do not exceed 1,500 microcuries. This method has the advantage of a more gradual approach to the ultimate radiation level. Moreover the effect of the initial doses may give an indication of the response and tolerance of the patient to P^{32}, and thus will provide a means of determining what radiation level will be required; (3) *the fractional method* consisting of equal fractions of 1 to 1·5 millicuries at intervals of one or two weeks. Treatment is continued until the desired effect is attained.

The involved nodes in lymphosarcoma have been shown by tracer studies to concentrate radiophosphorus to a relatively high degree. This fact constitutes the rationale for treatment of this condition with P^{32}. Results reported from different centres, however, show variable effectiveness of the treatment. Some cases of lymphosarcoma make a satisfactory temporary response to P^{32} therapy. Regression of enlarged nodes, disappearance of ascites and other

clinical signs have been observed. Lymphosarcoma is a protean disease and the variability of results of P^{32} treatment may be explained by the fact that P^{32} uptake by involved glands is very variable. It is necessary to carry out uptake studies on patients with lymphosarcoma before instituting P^{32} treatment. If uptake is high it is probable that P^{32} will give some temporary benefit. If it is low, neither P^{32} nor X-ray will produce any benefit.

The same considerations apply to Hodgkin's disease, mycosis fungoides, and multiple myeloma. If P^{32} is employed in the treatment of any of these diseases, careful fractionation of dose will prevent the occurrence of anæmia, leucopenia, and thrombocytopenia. However, in general I do not advocate P^{32} in the treatment of these conditions except in selected cases.

In polycythæmia vera it is now the general consensus that P^{32} is the treatment of choice. The method of treatment now in general use is the intravenous administration of 5 to 6 millicuries in a single dose. Six to eight weeks later this may be followed by a second similar dose depending on the hæmatological picture at that time. In some cases a single dose produces a complete remission. More often two doses of equal size are necessary, and, rarely, a third dose three months after the first is required.

A minor modification of the single large dose technique consists in dividing the dose into two or three equal fractions which are given on succeeding days. In this way less P^{32} is lost by excretion, and radiation sickness is avoided.

Hæmatological response to P^{32} treatment may not be anticipated in polycythæmia vera for four to six weeks and it may be delayed as much as three months. This latent period is of course due to the long life-span of erythrocytes. Radiophosphorus apparently affects only erythroblasts and therefore the effect of treatment becomes evident only when erythrocytes which would have resulted from these erythroblasts fail to appear in the circulation.

The question has been raised whether P^{32} is more likely than other forms of therapy to result in the development of leukæmia in patients with polycythæmia vera. Myelogenous leukæmia is known to be a frequent complication in either treated or untreated polycythæmia vera. There are many examples in the literature of development of leukæmia in polycythæmia patients whose only treatment was phenyl-hydrazine, Fowler's solution, or venesection. A more reasonable explanation of incidence of leukæmia in polycythæmia patients who have been treated with P^{32} is that any polycythæmia patient who does not succumb to cardiovascular accident or disease will terminate in leukæmia. Radiophosphorus produces longer and more complete remissions of polycythæmia vera than other forms of treatment, and so prolongs the life of the patient. This may result in the incidence of more deaths from leukæmia as a natural terminal development of the disease, wholly unrelated to treatment with P^{32}.

Evaluation of the dose effect relation when P^{32} is administered internally requires information concerning energy dissipated in various tissues. Marinelli, Evans, Mayneord, Bush and others have developed formulæ for calculation of energy accrued by the tissues due to a single dose of P^{32}. According to these calculations—1·1 microcurie P^{32} destroyed per kg. body-weight = 1 rep. 1 microcurie P^{32} uniformly distributed in a subject weighing 70 kg. will deliver 0·6 rep or grm.r/grm. in twenty-four hours.

These calculations apply only to a biologically inert system, since they assume uniform concentration and retention to complete decay of the dose administered. Experimental evidence shows, however, that phosphorus is not uniformly distributed in the body. On the contrary there is constant flux due to exchange and interchange of the metabolite among various tissues, as well as the daily loss due to excretion. There is no method yet known whereby the biological flux of phosphorus in the body can be measured. The rate of clearance from blood, excretion in the urine and fæces can of course be measured. From the amount lost by excretion, the total amount remaining in the body at any given time can be calculated.

The distribution of P^{32} in various body tissues is known from biopsy and autopsy studies. In general bone shows the greatest avidity for phosphorus, and is followed in order by spleen and liver. Within six to twenty-four hours after the administration of single or multiple test doses of 4 to 9 microcuries per kg. body-weight, when the P^{32} is given in the form of Na_2HPO_4, concentration in liver, spleen and bone is four to six times greater than in muscle, fat and skin.

After seventy-two hours, concentration in bone, spleen and liver is six to ten times that in muscle, fat, and skin. At certain intervals the concentration in bone and spleen and liver may differ, but the uptake in these tissues is always of the same order of magnitude, and, taken together, is about six to ten times as great as in all other tissues. Bone, spleen and liver, which for convenience we may designate "the bone compartment", constitute 10 to 12% of the body-weight. These tissues are all affected by anything which affects the hæmatopoietic system. The dose-effect relation can be evaluated only if the dose estimation is based on the differential distribution of the retained amount of the isotope. Following

determination of the retained amount of P^{32} it is assumed that after the equilibration period of three days, a 10 to 1 ratio is established between the bone, spleen and liver compartment, and the muscle, fat, and skin compartment. These assumptions may be subject to certain theoretical criticisms. First, the 10 to 1 ratio represents a maximum rather than an average. In clinical practice, however, it is advisable to use such a maximum since it ensures safety against damage of hæmatopoietic system. A second criticism may be made of the assumption of the existence of a 10 to 1 ratio on the third day, since actually the ratio is reached gradually over a longer period. Again in practice, however, this error is negligible and would not justify undertaking the very complex mathematics required for precise determination of the ratio on each day.

The advantages of this method of dose estimation are first, that it takes into account the factors which characterize an active biological system; second, it gives a better indication of accrued energy within the tissues; third, it affords a better correlation of the physical dose with the biological effect; fourth, it provides greater insurance against excessive irradiation; fifth, it affords a sounder basis for the comparison of radiation doses from X-rays and radio-isotopes.

Without entering into the details of dose calculation by this method, it must be emphasized that the weight of the patient is a primary factor in establishing the bone compartment—soft tissue compartment relation. For clinical use four dose record forms have been devised to cover patients in the weight range of 40 to 90 kg., with appropriate correction factors for ages falling within four major groups. From the dose rate figures the daily and cumulative soft tissue and bone compartment dose can be calculated, as well as the total body integral dose. Due to the difference of concentration ratio the energy accrued in the bone compartment is nine times greater than that in the soft tissue compartment.

This method of dosage estimation places radiophosphorus therapy on a firmer basis, and provides a means of correlating external and internal radiation therapy.

The radio-isotope which has attained greater prominence as a therapeutic agent during the post-war years is radioiodine. The first experimental attempts to treat hyperthyroidism with I^{131} were reported in 1941–42. It was not until after World War II, however, that carrier free I^{131} became available in abundance and radioiodine therapy of hyperthyroidism became widespread.

Many hundred cases have been reported in the literature, and various plans of treatment have been advocated. Review of the literature offers abundant evidence that radioiodine is an effective means of producing remissions in hyperthyroidism.

Investigators at the University of California Hospital have analysed their results in 100 consecutive cases treated between September 1945 and October 1949. Of the 100 patients 89 received what was considered a complete course of I^{131} therapy. 13 patients were men and 87 were women. 24 patients were under 25 years, 58 were between 26 and 50 years, the remainder were over 50 and 3 of these were over 65 years.

Of the 100 patients 49 had had one or more kinds of treatment for thyroid disease (12 surgery, 29 Lugol's, 11 propylthiouracil, 7 thiouracil, 3 X-rays, 9 thyroid by mouth).

Of the 89 patients who received full courses of treatment, 84 were considered clinically well. Reports reflect decrease in size of thyroid to normal; return of B.M.R., protein-bound iodine, cholesterol, and galactose tolerance to normal; normal uptake of radioiodine by the thyroid gland restored.

5 of the 89 patients developed hypothyroidism and are under treatment for that condition, 8 patients developed mild hypothyroidism but they do not require specific medication. 3 patients are receiving thyroid medication for exophthalmus.

This analysis is typical of reports from other centres. All reports contain some reference to initial exacerbation of disease following radioiodine therapy, and to incidence of hypothyroidism amounting to about 7 to 10% of all cases treated.

There is no uniformity in the dosage used in radioiodine treatment of hyperthyroidism, nor with regard to the number of treatment courses which may be given. In the various centres, doses have ranged from 2 to 29 millicuries, and the number of courses has varied from one to four.

Attempts have been made repeatedly to calculate the dose in terms of energy accrued by the thyroid gland. Such calculation is possible only if the following points are ascertained: Weight of the thyroid gland, distribution of the isotope within the gland, total amount of the isotope decayed in the gland. In clinical practice it is justifiable to make the following assumptions: that the weight of the thyroid gland is known, that distribution of the isotope within the gland is uniform, that all beta particles are utilized within the thyroid gland. Actually the amount of I^{131} which decays in the gland can be determined from the uptake curve. In some instances the loss of iodine from the gland is at a constant rate representing

an effective half-life of the isotope within the gland. Since there is a wide spread of effective half-life in different patients, it is important to determine the EHL for every patient. This requires that an uptake study be carried out for a period of four or five days to demonstrate collection and release of iodine by the thyroid.

At the University of California Hospital at present the amount of I^{131} necessary to deliver 6,000 r to the thyroid gland is calculated from the uptake curve for the test dose and from the thyroid weight. This amount is given as an oral dose. Since the uptake curve for the therapy dose may vary from the one obtained for the test dose, a complete uptake curve is made for the therapeutic dose. On the basis of this curve the radiation received by the thyroid gland is recalculated. Six weeks after the initial treatment dose an uptake curve is made with a test dose of I^{131}. If necessary the patient is re-treated and the dose is determined as before. About twelve weeks after initiation of therapy an uptake curve is made again after a test dose and therapy is given if indicated.

One important factor in successful treatment with I^{131} is the selection of cases. It is now generally accepted that only patients with diffuse hyperplastic glands should be treated. Patients with nodular goitres should not be treated with radiation. It is generally felt, also, that patients should be above 45 years, because of the theoretical possibility of late malignancy as a result of radiation.

Radioiodine was widely adopted for the treatment of hyperthyroidism on the premise that its use would obviate the problems encountered in X-ray therapy. These are, of course, skin erythema, reaction on the laryngeal mucosa, initial exacerbation of disease symptoms, and development of myxœdema. With the exception of skin effects every one of these reactions is known to occur with I^{131}. Moreover, when X-ray therapy is applied skilfully these sequelæ can be avoided. The results of external radiation therapy of hyperthyroidism compare favourably with the results of any other method of treatment. Also it must not be forgotten that with radioiodine the whole body is subjected to some radiation, though, with the dosage levels used in the treatment of hyperthyroidism, it must be admitted that no untoward hæmatological effects have been observed in patients who have been followed for a five-year period.

As we have observed previously, functioning thyroid tissue only concentrates iodine. For this reason relatively few forms of thyroid carcinoma are amenable to I^{131} treatment. Benign metastasizing struma with orderly follicular arrangement and presence of colloid has been shown to concentrate iodine to an appreciable degree. However this condition constitutes only about 15% of all neoplastic thyroid lesions. Wherever function can be stimulated in non-functioning thyroid tissue I^{131} can be used with remedial effect. This knowledge has been useful in treating metastases from thyroid carcinoma with I^{131} and a variety of methods have been used to stimulate thyroid function. These include propylthiouracil, thyrotrophic hormone, surgical and radiological removal of the thyroid gland. The presence of functioning thyroid metastases may be demonstrated by surface measurements over the lesions, following a test dose of I^{131}. If such measurements indicate function, therapeutic amounts of I^{131} can then be administered. The literature contains reports of treatment of such cases with temporary benefit. In general, doses used in the treatment of thyroid carcinoma must be several hundred times larger than those used in hyperthyroidism. However, no pattern of dosage for thyroid malignancies has been suggested.

At the University of California Hospital 64 patients with neoplastic thyroid disease have been studied for uptake of I^{131}. Only 3 of the patients showed sufficient uptake to justify a therapeutic trial. Attempts to stimulate function in thyroid carcinoma were all unavailing. Two of the patients who were treated received 500 and 600 millicurie doses respectively. The total doses in both cases were given in individual doses of 100 millicuries at intervals of one month. The patients became profoundly myxœdematous. In one patient a mass in the pharynx disappeared under treatment, but biopsy showed that tumour was still present in the area where the mass had been. The other patient showed no regression of multiple pulmonary metastases. Although some dramatic improvements have been reported from the treatment of thyroid carcinoma with I^{131} it is clear that the efficacy of this therapy is far from established.

It is my hope that in this brief review of radio-isotope research I have been able to show that artificial radio-isotopes have an established place in clinical radiology. No longer may we think of them simply as a means of experimentation. In the hands of radiologists the isotopes have an acknowledged place in the diagnosis and treatment of disease. It would be quite wrong, however, to suppose that in the radio-isotopes we have found the answer to all our diagnostic and therapeutic problems. Rather, through proper understanding of their nature and their biological effects, which subjects are the particular province of the radiologist, radio-isotopes may increasingly take their place as one important tool among the various tools which the radiologist already has at his disposal.

Section of Dermatology

President—W. N. GOLDSMITH, M.D., F.R.C.P.

[*February* 15, 1951]

Eosinophilic Granuloma of the Skin.—I. B. SNEDDON, M.B., Ch.B., M.R.C.P.

Mrs. L. H., aged 61. She complains of a reddish-blue thickened patch in the right pre-auricular area which began as a small spot four years ago, and has slowly enlarged, causing at times slight irritation. Apart from dyspeptic symptoms she feels well.

Family history.—Nothing relevant. She has one daughter aged 30. Her husband is alive and well.

Previous history.—Cholecystectomy four years ago. Since then she has had fat dyspepsia which was investigated in January 1950, when a barium meal showed a small para-œsophageal hernia. She was advised to take magnesium trisilicate and tinct. belladonna. She has taken no other drugs.

FIG. 1.—The plaque in front of the right ear. The photograph shows well the dilated follicular openings which are a characteristic of eosinophilic granulomata.

On examination.—In the right pre-auricular region there is an infiltrated slightly raised plaque 3 cm. in diameter of a bluish-red colour with dilatation of the follicles over the surface (Fig. 1). General physical examination revealed no abnormality other than a blood pressure of 180/105.

Investigation.—Blood count on January 4, 1951: Hb 85%—12·6 grammes%; erythros. 4,800,000/c.mm.; C.I. 0·89; M.C.D. 7·2 μ; leucos. 8,000/c.mm.

Differential leucocyte count: Band cells 5%—400/c.mm.; polys. 59%—4,720/c.mm.; lymphos. 20%—1,600 c.mm.; monos. 4%—320/c.mm.; eosinos. 12%—960/c.mm.

There is a slight absolute eosinophilia.

Blood Wassermann and Kahn negative.

X-ray of skull: No bony lesion.

X-rays: Long bones, including hands, show normal bone architecture. Heart a little enlarged to the left—no abnormality of the lung fields. Mantoux test 1/1,000 was positive.

Marrow biopsy (Dr. E. K. Blackburn).—The marrow was obtained with ease and the smears appear cellular. The erythron is normoblastic, while the leucon shows an eosinophilic reaction which appears to be somewhat unusual in type. Eosinophil premyelocytes are present, and some eosinophils are amphophilic. The thrombon is well represented.

The only abnormality is a somewhat unusual eosinophilic reaction. I have seen a similar one recently in a child with eosinophilic granuloma of bone, the smears being taken from an area of bone not radiologically involved. So far as I am aware, there is no comprehensive survey of bone-marrow smears in eosinophilic granulomatosis in the literature.

Histology (Dr. L. C. D. Hermitte).—The epidermis is generally of normal thickness but the rete cones are largely absent and, where present, they are short and narrow. There is a well-marked layer of collagen immediately under the epidermis of equal thickness to the latter, which shows no infiltration with inflammatory cells. A marked contrast with the rest of the corium which shows thick infiltration of a pleomorphic collection of inflammatory cells consisting of histiocytes, neutrophil polymorphs, eosinophil polymorphs, mast cells,

plasma cells and lymphocytes. On the whole this infiltrate is diffuse but under low power it can be seen to be more concentrated perivascularly. The vessels thus involved are either capillaries or very small arterioles and their endothelium is swollen and their walls appear thickened by a loose concentric arrangement of collagen. The eosinophils are more concentrated in some foci than in others but they are generally scattered loosely amongst the other cellular infiltrate.

Comment.—This case appears to be another example of the localized facial granulomata with a predominantly eosinophilic infiltrate which have been reported in the last few years in England by Wigley (1945), Borrie (1950) and Rook (1950), and in America by Buley (1946), Lever (1947), Lever *et al.* (1948 and 1950), Oliver *et al.* (1949), and Cobane *et al.* (1950). The patient shows the characteristic reddish-brown and purplish, thickened but soft, plaque situated on the face, which is the only site in which so far this condition has been described. The lesion shows well the prominent follicular openings commented on by Lever (1947). The case differs from all other reported cases in showing a raised eosinophil count in the peripheral blood and an eosinophilic change in the sternal marrow.

Histologically the infiltrate, which is made up of histiocytes, polymorphs, plasma cells and eosinophils is grouped mainly around the capillaries and these show swelling and degenerative changes in their endothelial cells. This suggests that the primary damage may occur in the blood vessels and that the condition is a degenerative or inflammatory disease of the cutaneous blood vessels rather than a true granuloma.

POSTSCRIPT (9.4.51).—3 doses of X-rays 100 r have produced no alteration in the lesion.

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Dr. I. W. Whimster: The lesion is composed of perivascular foci of severe, fibrinoid connective tissue degeneration and inflammatory cell infiltration affecting the walls and supporting tissues of all the vessels in the dermis save the capillaries of the papillæ and the larger vessels in the deepest layer of the dermis. The foci are often confluent but still obviously perivascular in origin. Among the inflammatory cells present are numerous eosinophils.

The name "eosinophilic granuloma" seems unfortunate since granulation tissue plays no part in the structure of the lesion, which appears rather to be a vascular and perivascular degeneration and inflammation, resembling in some respects that seen in erythema multiforme and polyarteritis nodosa.

Poikilodermia and Mycosis Fungoides.—E. WADDINGTON, M.D., M.R.C.P.

H. E., a printer, aged 42.

Duration of generalized eruption: twenty-five years.

At the age of 17, the patient developed a faint red, non-scaling, non-irritating rash on the chest and axillæ. Four years later this spread to involve the sides of the neck and the ante-cubital fossæ. Sixteen years ago similar lesions appeared on the thighs and in the popliteal fossæ.

He was shown to the Dermatological Section by Mitchell-Heggs, G., and Jacobsohn, F. W. (*Proc. R. Soc. Med.*, **29**, 717), in 1936 as a case of poikilodermia, and at that time the lesions affected the side of the neck, axillæ, epigastrium, popliteal and ante-cubital fossæ. There were also erythemato-squamous patches on the chest, back and abdomen.

A biopsy report in 1936 stated: "In the upper third of the dermis, there is a dense infiltrate of round cells lying in an œdematous reticulum. Histiocytes and chromatophores are also present. This infiltrate extends upwards into the papillary body and shows a moderately sharp lower border. There is only scanty elastic tissue in the area occupied by the infiltrate, but beneath this area no elastic changes were observed."

In 1936 he was treated with thorium X with some improvement, but this was not maintained.

When seen six weeks ago, the patient had noticed little change until seven months ago, when generalized irritation occurred for the first time, and "swellings" appeared in the left axilla and on the left side of the chest. These subsided in about three months, but new lesions appeared on the abdomen, left arm and right axilla. Throughout his health has been good, and he is gaining weight.

On examination.—There is a widespread eruption affecting both sides of the neck, shoulders, axillæ, arms, chest, back, abdomen and thighs.

The lesions on the neck, axillæ and right thigh resemble a chronic radiodermatitis with atrophy, pigmentation and telangiectasia. On the arms and trunk the lesions are bright red, with adherent scaling, small hæmorrhages and telangiectasia. The affected skin is atrophic. In addition, there are light brown erythemato-squamous patches on the back over the scapulæ and on the front of the chest. On the right axilla, left upper arm, left chest and abdomen are cyanotic infiltrated plaques. The lesion on the abdomen has recently ulcerated.

Lymph glands: There is bilateral enlargement of the inguinal glands, but no lymphadenopathy elsewhere.

Investigations.—X-ray chest normal.

Blood: Hb 104%; W.B.C. 11,850; neutros. 67%; lymphos. 22%; monos. 11%.

Biopsy report (Dr. I. W. Whimster).—From left upper chest area of poikilodermia: Epithelial depigmentation and slight hyperplasia and superficial dermal and epidermal infiltration by inflammatory cells. There is also some superficial vascular dilatation, and elastic tissue has disappeared from the upper third of the dermis. The appearances are compatible with the diagnosis of a premycotic eruption.

Biopsy from infiltrated plaque on right side of abdomen: Severe irregular epithelial hyperplasia and infiltration of the upper layer of the dermis by inflammatory cells of almost all types. The infiltrate freely invades the epidermis and extends downwards into the dermis along the line of vessels and appendages. The appearances are very suggestive of mycosis fungoides.

Comment.—In 1906 Jacobi described the first case of poikilodermia atrophicans vasculare, and in the same year Petges reported a case with identical skin changes in association with dermatomyositis. Since then, the name poikilodermia has been applied to a number of cases of dermatomyositis, and has led to a good deal of confusion. But in 1921, Lane described a case of widespread poikilodermia of twelve years' duration, in which there was no muscle weakness, and this patient died of Hodgkin's disease a year later.

Since 1921, there have been many similar cases reported in the Continental and American literature in which poikilodermia preceded by many years the appearance of a reticulosis (Oliver, 1936).

This case is interesting in that poikilodermia preceded the onset of mycosis fungoides by twenty-five years, and is one more case to support the belief that poikilodermia atrophicans vasculare is not a disease *per se*, but merely a stage in the development of a reticulosis, the most common being mycosis fungoides.

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Familial Benign Chronic Pemphigus.—H. HABER, M.D., and L. FORMAN, M.D.

Mrs. D. B., aged 49, complains of an irritating rash in the groins for twenty-three years. Has been treated in the past with X-rays and radium needles. The condition worsens in the summer months. The areas affected are the groins, armpits and under the breasts. Boils have occurred in these areas from time to time. Both groins and upper thighs show a sheet of flat lichenoid papules and discrete, slightly warty papules at the periphery. There was a simple intertrigo of the anal skin and under the left arm, a dry intertrigo of the left ear and a plaque of *fausse teigne* of the scalp. One finger showed a paronychia from which monilia was cultured.

Enquiry has elicited that one brother had had an affection of the groin.

It was thought that the condition was a lichenified infective eczema except that the outlying papules suggested lichen simplex. Some were horny and warty, resembling the primary lesions of Darier's disease.

There has been considerable discussion in the recent American literature as to the identity of Darier's and this disease.

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Dr. H. Haber: This condition is in my opinion a clinical entity. The histological resemblance to Darier's disease is only superficial. Besides, histological resemblance does not necessarily imply clinical identity. In two previous cases shown by B. Russell and myself (*Proc. R. Soc. Med.*, 1950, **43**,

558) I could produce a histological Nicolski, by rubbing normal-looking skin. The histology clearly showed an abnormal fragility of the epidermis in both cases. It is warmth, moisture and friction which expose the condition in its typical localization. Familial pemphigus is an inherited ectodermal defect.

Connective Tissue Nævus. Two Cases.—R. H. MEARA, M.B., M.R.C.P.

Case I.—D. I., a single woman, aged 37.

History.—In 1939, when 25 years old, she experienced a burning pain in the left shoulder and down the left arm, which was followed in a few days by a skin eruption on the left arm. This slowly spread to the left shoulder and left side of the back, and has since appeared on the left breast. The skin changes were similar to those present to-day and never consisted of blisters. Since the onset she has had recurrent attacks of pain in the affected area of the skin and in both shoulders. The eruption has regressed from the left arm but has slowly spread on the chest and left breast. The patient had a nervous breakdown at the age of 16 and again sixteen months ago, and she is at present under treatment at the West End Hospital for Nervous Diseases.

Present state.—The skin changes are confined to the left arm and the upper half of the left side of the chest, involving the left breast, axilla and scapular region (Figs. 1 and 2). On the

FIG. 1.—Connective tissue nævus Case I.

FIG. 2.—Detail of Case I.

back of the thorax they do not quite reach the mid-line. They consist of slightly raised, rather ill-defined areas, between 3 mm. and 20 mm. across, with an irregular surface, appearing to be made up of aggregations of small papules. This is most evident at the periphery of the lesions. They are flesh-coloured to light brown and are of the consistency of normal skin. No abnormality was found in other systems, including the central nervous system.

Histological examination.—A portion of the edge of a lesion with some normal skin was removed. In the affected part of the section there is slight thickening of the epidermis and broadening of the rete pegs. In the cutis the elastica is slightly irregular in pattern but no changes can be seen in the collagen.

Comment.—Clinically this case resembles the type of nævus usually known as the *connective tissue nævus*. Lewandowsky (1921) reported three such cases and suggested the name of "*Nævus elasticus regionis mammariæ*". Since then various other names have been given to it, including "cobblestone nævus", "zosteriform nævus", and "connective tissue nævus", which latter name is now generally accepted. Under this name Dr. Twiston Davies (1930) described two cases in which histological examination of the lesions showed absence of the elastic tissue and fragmentation and swelling of the collagen bundles. In one case there were

also lesions of the Pringle type of sebaceous adenoma. Steiner (1944) gives a comprehensive review of the literature, citing 37 cases, in addition to one described by himself. Clinically these nævi show two important features, one, the discrete papules, which when aggregated produce the "cobblestone" effect, the other, the systematized arrangement of the lesions, these being either in bands or in zosteriform distribution. The histological changes are usually confined to the connective tissue of the cutis and are often inconspicuous. Thickening, clumping, and homogenization of the collagen bundles occur in some cases, while in others there is breaking up and irregularity of the elastic fibres. The most that can be said of the changes in this case is that they are not incompatible with a diagnosis of connective tissue nævus. The similarity of the clinical features with those described under the name of the connective tissue nævus is sufficient for a firm diagnosis, despite the scant histological changes.

No reference could be found to any symptoms associated with this nævus and it is difficult to explain the pain experienced at its onset in this case, except as being due to an unconnected cause, which focused her attention on the skin condition.

Case II.—A. B., a schoolgirl aged 7.

The nævus has been present since birth, unaccompanied by any symptoms. It was noticed when the child was examined for another reason.

Present state.—On the right side of the upper half of the abdomen, extending down to the level of the umbilicus, and just beyond the mid-line, is a patch of altered skin (Figs. 3 and 4).

FIG. 3.—Connective tissue nævus Case II.

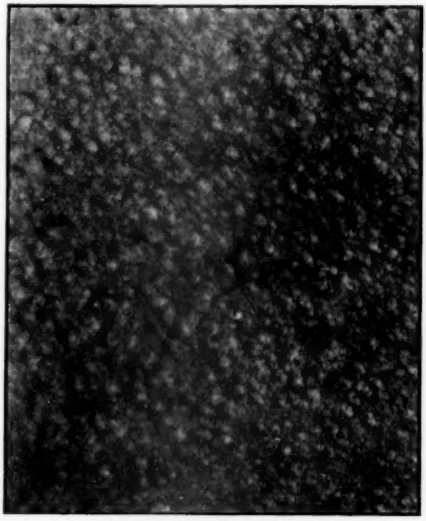

FIG. 4.—Detail of Case II.

The changes consist of small and very slightly raised papules and streaks. These are flat-topped and rather shiny, giving the impression of lichenification, and some have a brownish spot in the centre. The whole lesion is faint dirty brown.

Comment.—Unfortunately permission for a biopsy was refused by the parents, but the clinical picture suggests a diagnosis of connective tissue nævus.

I wish to thank Dr. W. N. Goldsmith for kindly allowing me to publish these cases.

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DR. F. PARKES WEBER: I agree that a condition of this type should be termed a connective tissue dysplastic nævus of the skin and/or subcutaneous tissue.

The following cases were also shown:

Median Mental Sinus.—Dr. C. H. WHITTLE and Dr. A. LYELL.

Sarcoidosis.—Dr. G. M. WAUCHOPE (introduced by Dr. H. W. ALLEN). (*See Proc. R. Soc. Med.*, 1950, **42**, 896.)

Polyarteritis Nodosa Treated with ACTH.—Dr. R. J. CAIRNS (for Dr. G. B. MITCHELL-HEGGS and Professor G. W. PICKERING).

Leukæmia Cutis.—Dr. L. SEFTON (for Dr. W. J. O'DONOVAN).

A Form of Ehlers-Danlos Syndrome.—Dr. M. Q. BIRKBECK (for Dr. W. S. TEGNER) introduced by Dr. P. S. HALL-SMITH.

(These cases may be published later in the *British Journal of Dermatology*.)

[*March* 15, 1951]

Primary Tuberculosis of the Skin.—D. E. SHARVILL, M.R.C.P. (for SYDNEY THOMSON, F.R.C.P., M.D., F.R.S.Ed.).

Jacqueline, aged 20 months.

A "pimple" appeared on the upper lip in October 1950 which ulcerated after two weeks, then improved with ointment. The parents and the family doctor considered this to be a septic spot and did not worry about it.

In February 1951 a lump appeared in the neck for which specialist advice was sought. The surgeon suggested the tuberculous nature of the gland and sent the child to the E.N.T. surgeon, who considered the tonsils normal, and also to the Skin Department.

Family History.—Grandfather, who lived in the same house, died one month ago of pulmonary tuberculosis; he was fond of the child and frequently kissed her. An uncle also has pulmonary tuberculosis. The parents' chests are radiologically normal.

On 28.2.51 there was a slightly raised lesion on the upper lip $\frac{3}{4}$ in. $\times$ $\frac{1}{2}$ in. of dusky erythematous colour. The surface was smooth and the edges sharply demarcated. At first sight there was little specific in its appearance, but on diascopy several areas of an apple jelly colour were evident. There was a firm painless gland of pea size under the right mandible, not fixed to the skin or deep tissue.

A tuberculin jelly test was strongly positive. Chest X-ray was normal.

On March 7 the skin lesion had lost its erythematous colour, and a few outlying yellowish follicular papules had appeared.

The gland, however, had greatly increased in size and was fluctuant, with red scaly overlying skin. It was aspirated, and large numbers of acid-fast bacilli found. The skin lesion was scraped gently and material examined directly, with negative result; culture and guinea-pig inoculation were also negative.

Now the skin lesion is smaller and of less frankly tuberculous appearance, and the gland is subsiding.

No treatment has been given, except aspiration of the gland.

Dr. L. Forman: There seems to have been an unusually long period of time—four or five months—between the appearance of the ulcer on the lip and the gland. These cases are very rare, and I do not think I have seen more than two.

Dr. D. E. Sharvill: The children's department of King's College Hospital has seen several cases of primary tuberculous ulcers in the last two or three years, but we have diagnosed none in the Dermatological Clinic.

Dr. R. E. Bowers: I saw a child aged 2 with an ulcer on the side of the face. There was a neat little chain of lupus nodules along the lymphatics between the ulcer and the gland. I treated her with calciferol and the condition cleared up entirely. She was observed for about three years afterwards.

Dr. J. Sommerville: These cases are exceptionally rare. During the last eighteen months we have had 2 cases at the Western Infirmary, Glasgow, that were distinctly comparable with Dr. Sharvill's case, going through the same processes, and both cleared up with calciferol treatment. At a meeting of the North British Society in Newcastle last year my attention was drawn to this question by a local pædiatrician, who produced 4 cases.

Dr. D. S. Wilkinson: We had a child at St. Peter's Hospital, Chertsey who developed a similar primary lesion at the age of about 3 months. First there was an ulcer and then the cervical gland became large and soft and aroused our suspicions. We treated the child with calciferol. The gland gave trouble for a long period but we aspirated it and eventually it cleared up. The ulcer had healed earlier.

In another case seen at Amersham Hospital the lesion began as soon as the baby had left the nursing home. The first indication was the development of troublesome enlargement of the glands in one groin. The lesion which was present on the thigh was not diagnosed at the time but it subsequently became lupoid and the child later developed a further ulcer on the arm which also became lupoid. We cultivated Koch's bacilli from it on two occasions. There was one case shown here by Dr. Sherry-Dotbridge (*Proc. R. Soc. Med.*, 1949, **42**, 138) in which a primary lesion became lupoid. I do not think that pædiatricians and chest physicians find these cases as rare as we do.

The President: Do pædiatricians and chest physicians usually leave these cases untreated? I was rather surprised to hear that they generally cleared up.

Dr. D. S. Wilkinson: I think the practice varies. They like to keep young children under observation, and older children are treated with streptomycin now.

Dr. J. Sommerville: We must remember that these lesions begin as a small nodule, which breaks down centrally with the edge raised, and then changes to a lupoid appearance.

The President: I had such a case in a child aged 2 in which the tuberculous chancre, which was on the scalp, continued to extend during a period of six months. It was not until after calciferol treatment was started that the lesion began to heal. After eight weeks' treatment it had healed completely.

Dr. J. Overton: I have seen 2 cases in the last two years. The first, two years ago, was a child who had been in Iraq where she was supposed to have suffered an insect bite on the right knee. This became sore and was associated with a marked inguinal adenitis. The condition was treated abroad as a pyogenic infection. I curetted the local lupus lesion and supplemented this with an intensive course of calciferol therapy. A month later satisfactory healing had occurred and the associated adenitis had disappeared. There has been no relapse. A more recent case was in a schoolgirl who fell and abrased her knee, following which she developed inguinal adenitis. This was inadvertently incised. When she came to see me she had a florin-sized plaque of lupus vulgaris over the area of the injury with marked associated adenitis. Treatment has only just commenced.

Dr. D. I. Williams: Primary tuberculosis affecting the lung usually clears up unnoticed and it seems reasonable that spontaneous cure might also happen in the case of the skin. I can understand that the parents may demand that something should be done and it may be reasonable to give calciferol; but I should be a little afraid of giving streptomycin in a case where the child was happily building up his immunity; the immunity might be destroyed and should the disease become generalized one would not have this very useful weapon to employ. I should be opposed to the immediate use of streptomycin, but I might use calciferol.

Dr. F. R. Bettley: I agree that a large proportion of these cases clear up, but some of them develop very serious pulmonary disease. I should be unhappy to see this child not treated. There is no good evidence of localization, and I think it would be wrong to withhold treatment when the child may be faced with a fatal spread of the disease.

Dr. J. Overton: I know of no one who has had any consistent success in the use of para-amino salicylic acid either locally or by mouth for skin tuberculosis. I have tried it repeatedly without any success. With regard to the question of immunity and the use of streptomycin I know of no satisfactory evidence to show that the giving of this antibiotic reduces the tendency to develop immunity.

Dr. D. I. Williams: The child might well be treated now with calciferol or P.A.S. I would not give her streptomycin now, because, supposing it were given and failed or the organisms became resistant to streptomycin, the streptomycin would then be of no use at all if the disease generalized.

Dr. Alice Carleton: According to Wiener (1947, Skin Manifestations of Internal Disorders, London, p. 180), approximately 1 out of 750 cases of tuberculosis starts in the skin.

Leprosy.—D. S. WILKINSON, M.D.

Paul H., 6 years 11 months.

This boy was born and brought up in Bengal. He came to England eighteen months ago. About this time (when aged 5½) he developed several scaly, white patches on his face. These appeared and disappeared but became more persistent on arrival in England.

Past history.—Measles and chickenpox, aged 4–5. No unusual illnesses in childhood.

Family history.—Mother well. Father has leukæmia. Brother and sister both without skin disease. Brother at present has a cough which is being investigated. All the family have been examined and no skin or nerve lesion found.

Leprosy was prevalent in Bengal, both endemic and being contracted (according to the mother) by European residents there. A neighbour, who had some contact with the child, had been treated and "cured" of this condition before he came to live next to this family. No other particular contact sources of possible infection known.

On examination.—When first seen, four months ago, the boy appeared to have multiple patches of pityriasis alba scattered over the cheeks. These were treated and all but one patch had practically disappeared when seen again a month later. This one patch, however,

raised the question of leprosy clinically, and the patient was found to be anæsthetic to light touch in this area. The great auricular nerve was palpable.

The lesion then was less pronounced than it is now, smaller and somewhat flatter. The edge was a dusky purple-brown colour and scaly, and the centre paler than the rest of his skin, dry and pallid (Fig. 1). The boy noticed a sensation of pricking in the area in the early stages. The lesion became larger and the edge more infiltrated in the next two months, but is now subsiding. It presented, at its height, the classical "three zones" of tuberculoid leprosy:

FIG. 1.—Leprosy—solitary cutaneous lesion.

(1) Outer scattered, brown, pin-head-sized papules and nodules.
(2) Purplish-brown scaly raised margin, composed of an aggregation of these nodules.
(3) Central area of pale, dry skin free of nodules.

The great auricular nerve has become harder and more easily palpable, and can be seen as well as felt. I think that the right ulnar nerve is more easily palpable than the left, but no other nerves appear clinically to be enlarged. There are no other lesions apart from a few scaly lesions suggestive of pityriasis alba which can be seen on the face.

Investigations.—Mantoux test 1 : 1,000 negative. Hb 90%; R.B.C. 5,320,000; W.B.C. 6,710. Polys. 47, lymphos. 38, monos. 10, eosinos. 4%.

Lepromin test February 22, 1951. Positive flare in forty-eight hours followed by a papule which can be seen on the left forearm.

Biopsy (Dr. I. W. Whimster).—The dermis contains numerous well-defined tubercles. The appearances are compatible with the diagnosis of tuberculoid leprosy or tuberculosis.

The lesion is anæsthetic to light touch, not to pain. Thermal appreciation cannot accurately be carried out on this boy but appears to be diminished.

He has been having 50 mg. diamino-diphenyl sulphone by mouth daily, with iron and vitamin B for the last three months. The lesion is less pronounced than it was a month ago.

Comment.—The lesions had been present some nine months, so that the disease first appeared when the child was about 5 years old. In countries where leprosy is endemic, 10% of cases are said to begin in the fifth to tenth year. Muir reports a case in a child of 6 months. It is unusual to see affected children in this country, though I do not think the disease itself to be very rare in England.

In tuberculoid leprosy, the diagnosis has to be made on clinical grounds; biopsy may only indicate a tuberculoid structure—the best tubercles are said to be found in leprosy and bacilli are rarely seen in this form. The lepromin test, here positive, is only really helpful after the diagnosis has been made, to assist in prognosis. A positive reaction has occurred in healthy contacts among children living in endemic areas. The implication is that some degree of immunity has been acquired in these cases, but it has not been established how commonly this occurs or how specific the immunity is, even assuming that the reaction itself is specific.

I think that we should be cautious in assessing the value of sulphone therapy on short-term results, in view of the natural tendency of the skin lesions in the tuberculoid form to disappear or regress spontaneously.

Leprosy under Treatment with Diamino-diphenyl Sulphone (Two cases).—E. WADDINGTON, M.D.

Case I.—Lepromatous Leprosy.

C. G., aged 28.

The patient lived in Bombay until December 1948.

Thirteen years ago he bruised his shin and this was followed by recurrent ulceration at the site of the injury. Four years ago, he noticed anæsthesia on the lower third of the left leg. Eighteen months ago, he was seen by Dr. H. R. Vickers in Sheffield, and at that time there was an indolent ulcer on the anterior aspect of the left ankle, and a scaly pigmented area on the medial side of the ankle. There was constant anæsthesia to light touch and pin-prick on the lower half of the left leg.

Examination of nasal smears and of slit smears from this area were negative for acid-fast bacilli.

A biopsy from the anæsthetic area showed no abnormality other than heavy pigmentation of the basal layer of the epidermis.

A portion of the saphenous nerve was excised and showed the presence of acid-fast bacilli in the nerve with very little surrounding inflammatory reaction.

The patient has been attending St. Thomas's Hospital since November 1949. In December 1949 the lepromin test was negative, indicating a poor natural resistance, and this result combined with the poor cellular reaction in the nerve, suggested that this case would eventually develop into the lepromatous type.

For the past seventeen months he has received diamino-diphenyl sulphone, 300 mg. daily (initial dose, 100 mg. daily), and no change was noted until eleven months ago when he developed an ulcer following a biopsy from the left calf. This was accompanied by a low grade intermittent fever, and the rapid onset of gross œdema of the left foot and leg, extending up to the knee. At the same time, the pigmented scaly area became shiny, erythematous and infiltrated. This infiltration was succulent, and of the lepromatous type, in contrast with the firm infiltration of tuberculoid lesions. During the next month, the leproma spread in a broad band up the lateral side of the calf and extended to the popliteal fossa. There was a simultaneous extension of anæsthesia over this area, and severe pain was produced by light percussion over both malleoli. This lepra reaction subsided after six weeks.

A biopsy showed a heavy infiltration of the dermis with large foamy and sometimes necrotic histiocytes, lymphocytes, plasma cells and giant cells. The inflammatory cells were in places arranged in tuberculoid foci round vessels and sweat ducts. A small number of acid-fast bacilli were present.

Slit smears taken at the same time from the lobes of the ears, supra-orbital ridges, malar part of cheeks, arms, legs, back and buttocks, were all negative for bacilli.

Since the acute reaction eleven months ago, the infiltration has gradually diminished, and today there is a reddish-brown scaly lesion extending from the dorsum of the foot up the calf and on the lateral aspect of the calf, and anæsthesia is still present over the whole area. There has never at any time been any thickening or tenderness of nerves.

Biopsy report (2.3.51).—Fibrosis is occurring in and around the remains of the tuberculoid foci. The histiocytes of these foci have now ceased to be epithelioid and are less numerous. The appearances are those seen in lupus vulgaris under calciferol treatment.

Case II.—Tuberculoid Leprosy.

T. G., aged 24.

The patient was born in Bangalore, where he lived until three years ago.

The first lesion appeared five years ago on the right shin, and slowly increased in size until two years ago when treatment was commenced. He was shown to this Section in 1949 by Dr. K. M. Tomlinson, and the lesion on the right leg involved the whole of the medial and posterior aspect of the calf. This pigmented scaly area was anæsthetic to light touch, pain and temperature. In addition, the patient had recently developed new leprides which were reddish-brown, well-defined infiltrated plaques. Although hyperæsthetic in the early stages, they rapidly became anæsthetic. These were situated as follows: Left cheek and chin. Lateral aspect above the elbow. Dorsal surface of the penis. Anterior middle third of left thigh. Medial and posterior aspect of right calf and lateral side of knee. The left sole and medial side of the big toe.

Nerves: There was thickening and tenderness of the left great auricular nerve, the right ulnar nerve, the right lateral popliteal nerve, and the left medial calcaneal branch of the posterior tibial nerve.

There was anæsthesia of all toes and the medial half of the sole.

The lepromin test in February 1949 was strongly positive indicating a high natural resistance.

Biopsy of lepride on left thigh.—In all the layers of the dermis there are strongly demarcated foci of inflammatory cells, consisting of a central zone of histiocytes and a surrounding zone of lymphocytes. These foci are mostly perivascular or periglandular. There were no acid-fast organisms in the sections examined.

The histology, combined with the positive lepromin test, confirms the clinical diagnosis of tuberculoid leprosy.

Treatment.—17.1.49 to 5.4.49: Para-amino salicylic acid, 18 grammes daily.

While on this treatment new leprides were still developing.

5.4.49 to 28.2.50: Sulphetrone orally, commencing with 1 gramme daily, and gradually increasing to 6 grammes daily. This dose was reached on July 19, 1949.

28.2.50 and subsequently: Diamino-diphenyl sulphone, 100 mg. daily for two weeks; 200 mg. daily for two weeks; 300 mg. daily from the fifth week onwards.

The patient has had no toxic symptoms. Iron was administered with the sulphones.

Progress.—After two years' sulphone treatment, the majority of the smaller leprides have become atrophic. The penile lesion has completely disappeared, and the large lesion on the right calf has diminished in size and is no longer infiltrated. Sensation is returning over these areas.

Nerves: The only nerve which remains thickened and tender is the left medial calcaneal branch of the posterior tibial.

Sensation: The area of anæsthesia on the left foot has diminished and only involves the terminal phalanges. There is also impaired sensation to pain and temperature over the limbs. The patient has had a number of second-degree burns from a hot water bottle.

Biopsy report on 2.3.51 (from the same site as the original biopsy): A portion of skin showing slight superficial scarring and a non-specific perifollicular inflammatory reaction.

Comment.—These 2 cases represent the two main types of leprosy. The tuberculoid type has a strongly positive lepromin test, indicating a high natural resistance, and this is supported by the histology which demonstrates the effective tissue response. The lepromatous type, on the other hand, has a low resistance with a negative lepromin test, and an inadequate localizing cellular reaction in the affected tissues.

As far as treatment is concerned, it is impossible after only two years to assess the effect of the sulphones, particularly in the tuberculoid type, since these cases frequently improve spontaneously. But it may be significant that new leprides were developing before treatment commenced, and none has appeared since. In addition, regression in all lesions occurred within six months.

In the lepromatous case, the nerve biopsy, taken before treatment commenced, showed the presence of numerous bacilli with remarkably little surrounding inflammatory reaction and this finding, combined with the negative lepromin test, suggested that his natural resistance was extremely poor, and yet after eleven months' treatment the skin biopsy taken at the time of the acute reaction showed some attempt to form tuberculoid foci round the vessels and sweat ducts and the more recent biopsy demonstrates how effective the subsequent reaction has been. The histological picture now closely resembles a healing lupus vulgaris with fibrosis occurring in and around the remains of the tuberculoid foci, and there are no bacilli present.

This change from the lepromatous to the tuberculoid histology during sulphone treatment has been reported by a number of observers, and it has been suggested that in addition to their bacteriostatic effect the sulphones may stimulate the reticulo-endothelial system.

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Leprosy.—J. LUDER, M.D., M.R.C.P., D.C.H. (for J. R. OWEN, M.R.C.P.).

I. T., male, aged 10; born and lived in India until ten months ago.

History.—Six weeks ago left hand trodden on and bruised on ulnar side. Subsided, but followed after one month by red tender swelling over hypothenar eminence, little and ring fingers. This has persisted but diminished in degree and tenderness. One week later reddish patch appeared round garter mark on right calf and rapidly spread over most of back of thigh. Crop of papules, reddish and fleshy, appeared round the right wrist and both ankles. Clinically well, apart from short attack of influenza.

Family history.—One of 11 children. They and parents found to be free of leprosy.

On examination.—Positive findings: Left hand—brawny indurated swelling of hypothenar eminence and medial two fingers. Right lower limb—large reddish brown macule over back of thigh and calf. Surface scaly and edge definite and palpable.

Papular eruption on both ankles and right wrist.

C.N.S.: High ulnar palsy in left arm with gross thickening and tenderness of ulnar nerve at elbow. Thickened cutaneous branch of left radial nerve at wrist. Possible thickening of right popliteal nerve.

Investigations.—Blood, W.R. and Kahn—both positive.

Biopsy of skin from macule: aggregations of epithelioid cells around sweat ducts and hair follicles. Some giant cells. Consistent with tuberculoid leprosy. No *Myco. lepræ* seen.

Smears from undersurface of macule and nasal scrapings: no *Myco. lepræ* seen. Lepromin test strongly positive.

Treatment.—Oral Sulphetrone; at first 1 gramme daily increasing to 2 grammes daily.

Comment.—A fairly typical case of tuberculoid leprosy, in view of histology, absence of bacilli, definite edge of macule, nerve involvement and positive lepromin (Cochrane, 1946, *Leprosy Rev.*, **17**, 37). This is much the less common type in children. Its sudden appearance is probably due to trauma precipitating a reacting phase in a long-established condition. No source of contact known.

Keratosis Pilaris Associated with Myxœdema.—LOUIS FORMAN, M.D.

Miss V. J., aged 14 years.

Complaint of dryness of the skin of the body, limbs and hands for two years. Periods commenced at 13 years. During the past year she has lacked energy and has put on weight for three years. She feels the cold badly and the appetite is poor. The maternal grandmother had myxœdema.

Her face is pale, rounded and heavy lidded. The nose is broad, probably due to an old injury. The scalp hair line is set well back at the temples. The lanugo hair over the back and cheeks is thickened and dark.

The skin is generally dry and hyperkeratotic with slight ichthyotic scaling. This change is also seen over the flexures of the limbs (Figs. 1 and 2). Keratosis pilaris is present over the trunk and extensor aspects of the limbs. Her record at school is good. She was top of the

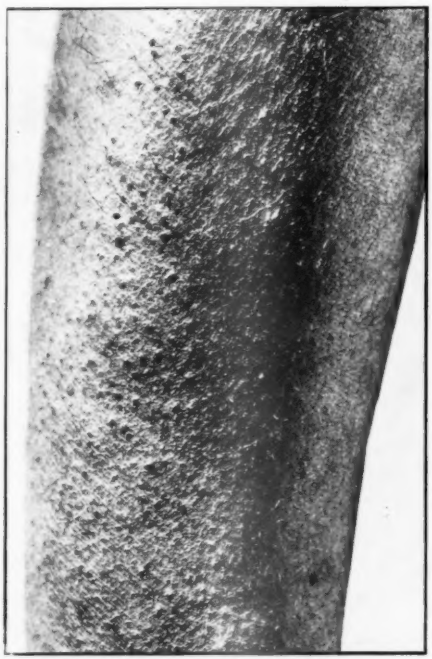

FIG. 1.—Keratosis pilaris of the arm

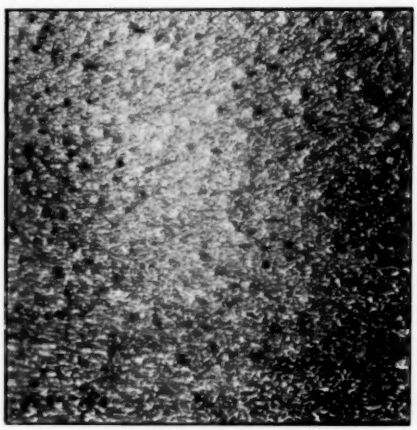

FIG. 2.—Keratosis pilaris of the abdominal skin.

class last year and won a scholarship. Her progress this year has been satisfactory except that she has become "rather slow".

Investigations on the Blood.—

β Carotene	358 mg./100 ml.	slightly increased
Vitamin A	42 i.u./100 ml.	slightly reduced (Dr. W. Merrivale).
Hb	70%	
Blood serum cholesterol 425 mg. per 100 c.c.		
B.M.R.	−47% (Dr. R. R. de Mowbray)	
	−37% (Dr. R. R. de Mowbray)	

Comment.—I have not been able to discover that keratosis pilaris has been described as a feature of myxœdema. The follicles might be expected to show early thyroid deficiency changes, as they do with vitamin A and C deficiency. It is known that in myxœdema there is inability to change carotene to vitamin A. The diminished blood level of vitamin A in this case may be responsible for the keratosis pilaris.

Dr. J. Overton: What significance does Dr. Forman attach to the fact that the patient's father suffered from a dry scaly condition of the skin? Is it not suggestive of congenital ichthyosis?

Dr. L. Forman: I do not think this child is suffering from congenital ichthyosis. The skin has only shown abnormal dryness for the last two years and the flexures are involved.

Dr. A. C. Roxburgh: Has this child had the keratosis pilaris only in the last year or two?

Dr. L. Forman: As far as we know, for two years.

The President: She also had a certain amount of erythrocyanosis frigida and complained a good deal of coldness of the limbs and hands. I think that keratosis pilaris is almost a constant feature of erythrocyanosis frigida. The worst case I have seen of that disorder developed big bullæ in the winter, and I had to take the patient into hospital for two consecutive winters. We estimated the B.M.R. on both occasions and it was at the upper limit of normal.

Dr. C. H. Whittle: I think it would be very interesting if Dr. Forman could later tell us the result of treatment and also note whether there is any change in the blood vitamin-A level after giving thyroid.

POSTSCRIPT (July 1951).—This child has been treated for seven weeks with up to 1 grain of dry thyroid a day and there has been marked improvement. She has lost weight, her skin is healthier, smoother and pink; she is more alert and responsive. The keratosis pilaris over the back has almost disappeared except for a band under the back strap of her brassière.

β Carotene is now 177 mg. and the blood serum cholesterol 220 mg./100 ml.

Serum protein bound iodine, 3 microgrammes % before treatment, is now 9 microgrammes %. —L. F.

The following cases were also shown:

Congenital Papillomatous Ichthyosiform Ectodermal Defect.—Dr. S. A. MASON (introduced by Dr. SYDNEY THOMSON and Dr. D. I. WILLIAMS).

Generalized Scleroderma with Sclerodactyly and Dermatomyositis Treated by Cortisone.—Dr. C. H. WHITTLE.

(These cases may be published later in the *British Journal of Dermatology*.)

Section of Neurology

President—W. Russell Brain, D.M., P.R.C.P.

[*January* 4, 1951]

A Case of Marchiafava's Disease

(Primary Degeneration of the Corpus Callosum)

By Turner McLardy, M.B.E., M.D.

Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, London

Forty-six cases of Marchiafava's disease have been reported in the clinico-pathological literature to date. Of these 44 were Italians by birth, 1 Swiss and 1 American. All were men, their ages at death ranging from 38 to 82 years (average 58). All but one were chronic alcoholics. The majority were addicted to crude Italian red wine and suffered from undernutrition. The duration of the fatal illness was usually between three and six years and the onset insidious. Remitting mental symptoms and pareses featured prominently in most instances.

The present case would appear to be the first encountered outside Italy and the U.S.A. The patient was an English publican, aged 58 at death, with no traceable Italian ancestry. Although probably an addict to whisky, rum and beer, there was no history of any taste for Italian wine or of nutritional deficiency. The onset of illness was unusually sudden and the course unusually rapid. Without any prodromata or apparent precipitating factor he awoke one morning with bizarre delusions of reference and rapidly became disorientated for time and place, auditorially and visually hallucinated and generally lethargic. Two weeks later he was observed to have no pupillary reaction to light, his limbs were becoming rigid in flexion and an X-ray photograph of his skull showed the clinoid processes to be less distinct than normal. Despite intensive vitamin therapy his general condition deteriorated progressively except for brief periods when he was less disorientated and less lethargic. By the end of the third month he had developed severe spastic paraplegia, double incontinence and bed-sores. He died in coma with bronchopneumonia five months after the onset of illness.

General post-mortem showed terminal bronchopneumonia, some fatty degeneration of the liver and brown atrophy in the heart. The leptomeninges of the brain were thickened below, and along either side of, the superior longitudinal sinus. Cerebral convolutions were slightly atrophied in the inferior parietal lobule and in posterior parts of the middle and inferior frontal gyri in both hemispheres. The centre of the corpus callosum (cut sagittally) appeared grey and necrotic.

Histopathological investigation revealed the appearance pathognomonic to Marchiafava's disease, namely selective demyelination of the central fibres of the corpus callosum, as well as additional bilaterally symmetrical lesions, which have been observed less consistently: demyelination of central fibres of the anterior commissure, the cingulate white matter, the brachium pontis and the isthmi of white matter between the centrum ovale and the parietal and frontal gyri of the lateral convexity. The most dorsal fibres of the optic chiasma were similarly affected.

More detailed investigation revealed that in the demyelinated regions axis cylinders were well preserved; myelin breakdown products were remarkably inconspicuous, compound granular corpuscles being scattered only sparsely in the (presumably most recent) lesions in brachium pontis and isthmal white matter; oligodendroglia and astrocytes were moderately proliferated with little deposit of glial fibres; isolated fibroblast-like spindle cells, previously described in this condition and certain cases of disseminated sclerosis, lay mainly along the axis of the nerve fibres and seemed most numerous in the (presumably oldest) lesions in corpus callosum, anterior commissure and cingulate white matter. A most striking microscopical feature was that blood vessels throughout the lesions appeared tortuous and proliferated and possessed walls very conspicuously thickened by reticulin and collagen. There were arteriosclerotic changes in the vessels of the white matter elsewhere, but these were of moderate degree.

Discussion was confined largely to the ætiology of the condition and focused especially on the resemblances to experimental lesions in commissural white matter produced in various species of animals by repetitive exposure to poisons such as carbon monoxide, cyanides and azides. Such substances have never been looked for in the liquors to which Marchiafava patients have been addicted. The bilaterally symmetrical non-commissural white matter lesions have so far never been described by experimental workers. Age and sex, apparently so significant in Marchiafava's disease and suggestive of a hormonal factor, have not been commented upon in such animal studies.

Selective demyelination in the dorsalmost portion of the optic chiasma has only once before been described in this condition and in that case also there was some defect in the light reflex of the pupils.

It was suggested that the dense fibrosis of the parasagittal leptomeninges and the evidence of erosion around the pituitary fossa, observed in the present case, might indicate that dorsal restriction of pulsatory movement of the brain played some part in determining the sites of the vascular pathology and demyelination.

(This case will be published elsewhere in fuller detail in collaboration with Dr. S. W. Hardwick.)

The Retina in Cerebrospinal Lipidosis

By J. G. GREENFIELD, M.D.

National Hospital, London

COMPARATIVELY few examinations of the retina in amaurotic family idiocy and other forms of cerebrospinal lipidosis have been made. It seems therefore worth while to demonstrate the histology of the retina in three cases of this kind, falling into three different age-groups, especially as the use of the new periodic-acid-fuchsin (Schiff) staining technique with celloidin sections has brought out certain points with special clarity.

Case I.—J. P., female. This was a typical case of Waren-Tay-Sachs form in a Jewish baby, showing the cherry-red spot and dying at about the age of 18 months. (The eye was examined through the kindness of Professor G. R. Cameron of University College Hospital.) Here the fovea was wider than normal measuring 860μ across its pit from one side to the other. There was also an unusually wide gap in the inner nuclear layer (400 μ). The layer of ganglion cells was much thinner than normal being only two to three cells thick on the rim of the fovea, instead of the normal four to five layers. The individual ganglion cells were swollen with very finely granular material which stained pink with the PAS technique. Most of the cells were about 20 μ in diameter. Many rounded cells, with an irregular, eccentric nucleus and cytoplasm filled with more deeply red-stained material were seen, especially in the deeper parts of this layer. Some were as large as 25 μ in diameter. An occasional cell of this kind lay against the inner surface of the inner nuclear layer. These cells were interpreted as being phagocytic. As one passed away from the fovea the swelling of the nerve cells became less, few exceeding 15 μ in diameter, and the more fuchsinophil cells in the deeper layers were even smaller. The inner and outer nuclear layers showed no abnormality. The lipo-protein in the outer segment of the rods and cones was stained a bright red colour by this technique (Figs. 1 and 2).

The PAS technique stains the 1·2 glycol grouping which may be present either in glycoproteins or glycolipids. It seems probable, from other evidence, that the material in the nerve cells in amaurotic family idiocy is a lipid, but it does not follow that the lipid in these cells is entirely glycolipid, as there may be an admixture of other lipids which do not stain or of inositol phosphatids which contain the required carbohydrate grouping and are therefore stainable.

Case II.—J. F., male, aged 4 years. (Under Dr. Purdon Martin in the National Hospital, Queen Square, W.C.)

The child had had convulsions for twelve months before death and had shown inco-ordination of cerebellar type for about eight months. On examination a few days before death there was considerable mental backwardness. He evidently saw, as he reached out to grasp objects held in front of him. No abnormality except slight pallor of the discs was seen ophthalmoscopically. Almost any form of stimulus brought on myoclonic jerking movements. The retina in this case showed much less swelling of ganglion cells, and no evident loss of these. None was more than 15 μ in diameter and most were less. Some contained fine granules, but these did not stain by the PAS technique and no phagocytic cells containing fuchsinophil material were seen in the layer of ganglion cells. The inner nuclear layer was normal. The outer nuclear layer was deficient over an area about 2 mm. in diameter centred on the fovea. In one section which passed through the fovea the outer nuclear layer on the temporal side came to an end 1·25 mm. from the centre of the fovea, but as the retina was rather folded on the other side, the corresponding gap on that side could not be measured. The rods and cones showed a corresponding loss. In the outer plexiform layer there were small accumulations of pigment from the neuro-epithelium and also a few rounded cells which contained fuchsinophil material as well as a few short rods of pigment in their cytoplasm. The outer segment of the rods and cones stained much less brightly in this case. No loss of the outer nuclear layer could be seen in other parts of the section which included the posterior half of the globe in the horizontal plane (Fig. 3).

FIG. 1

FIG. 2

FIG. 3

FIG. 1.—Foveal region of the retina in Case I. × 70. PAS stain. The pit is wider than normal, the gap between the ends of the ganglion cell layer being over 400 μ. The outer nuclear layer and the rods and cones are well preserved throughout. The outermost dark layer is the fuchsinophil lipo-protein in the outer segment of the rods and cones, as the retina is separated from the pigmented epithelium in this region.

FIG. 2.—A segment of the retina from the left (temporal) side of Fig. 1. × 350. The ganglion cells are swollen with finely granular lipid, staining faintly by the PAS technique. They form only two or three layers of cells, and numerous large, darkly stained, lipid-containing phagocytes are also present. The staining of the outer segment of the rods and cones is seen in more detail.

FIG. 3 (*Case II*).—Section of retina in foveal region. × 280. PAS stain. There is no obvious swelling of the ganglion cells which lie in five to six layers. The outer nuclear layer comes to an end near the centre of the photograph, and to the left of this several rounded cells containing fuchsinophil material are seen in the outer plexiform layer. The nuclei of the inner nuclear layer are shrunken and stain darkly, but this is probably due to post-mortem autolysis.

Case III.—E. I., male, aged 28. (Under Dr. Denis Williams at the National Hospital, Queen Square, W.C.)

This man had had epileptic attacks for fifteen years and some unsteadiness of gait for almost as long. For seven years he had had myoclonic jerkings of the legs and dysarthria. He had ceased to write owing to ataxia of the arms about eighteen months before death. When examined in hospital there was a mild degree of intellectual deterioration but no loss of vision was found nor could any retinal abnormality be seen. The retina in this case was normal except in the layer of ganglion cells which were slightly swollen, most measuring from 15 to 17 μ in diameter, and contained rather coarse granules which stained red by the PAS technique. Occasional larger cells, up to 25 μ, filled

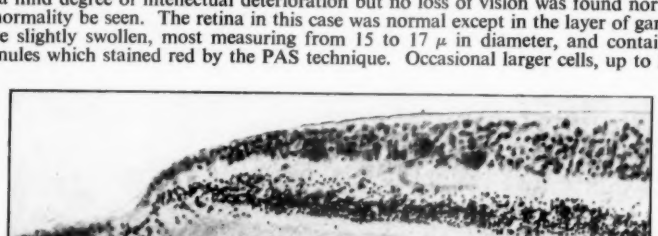

Fig. 4 (*Case III*).—Foveal region. × 120. PAS stain. All the cell layers contain the normal number of cells, but the ganglion cells are slightly swollen with granular lipid and a few darkly staining phagocytes containing fuchsinophil lipid are present in it.

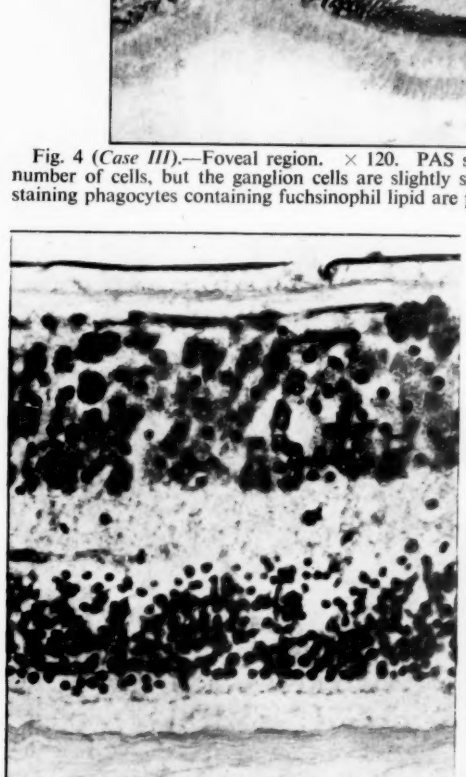

FIG. 5 (*Case III*).—Foveal region. × 350. PAS stain. To show details of the ganglion cells and phagocytes.

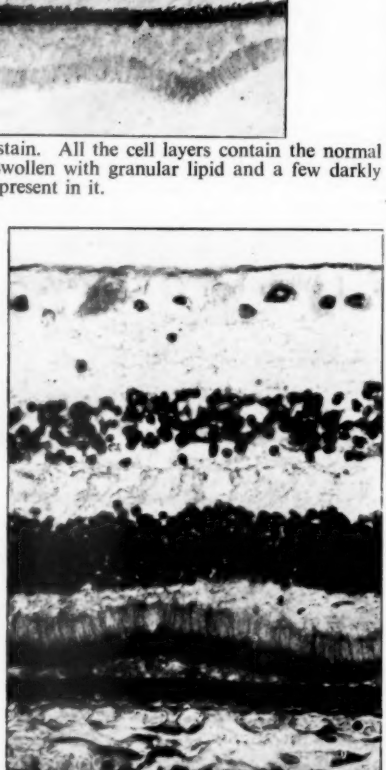

FIG. 6 (*Case III*).—Temporal retina, 4 mm. from centre of fovea. × 350. PAS stain. Here the appearances are almost normal. The staining of the outer segment of the rods and cones is seen here in almost normal relation to the layer of pigmented epithelium.

with more deeply fuchsinophil material were seen, but they were much less numerous than in Case I and could only be found near the fovea. The loading of the ganglion cells with granular material became less on passing from the macula, and at a distance of 4 mm. from the centre of the fovea, the retina appeared almost normal. The lipo-protein in the outer segment of the rods and cones stained fairly brightly in this case, especially in the peripheral retina where rods were more numerous than cones (Figs. 4, 5 and 6).

Discussion.—The changes found in the retina in Case I were similar to those found in previous cases belonging to the infantile or Tay-Sachs group (Hancock and Coats, 1911; Greenfield and Nevin, 1933), but there was more definite evidence of degeneration and disappearance of nerve cells near the fovea, and the PAS technique stained the material in the ganglion cells and phagocytic cells in a differential manner. In Case II also, the disappearance of the outer nuclear layer, along with the rods and cones, in the foveal region was similar to what has been previously reported in this age-group. In the younger cases (e.g. Bird's Case 2, aged 4 at death), as in this case dying at the same age, the loss was confined to the foveal region, whereas in cases surviving longer (Bird's Case 3, aged 9; Greenfield and Holmes, aged 13; Batten and Mayou, aged 6; Ichikawa, aged 7½; Stock, aged 9 and 7; Bielschowsky, aged 6) the outer nuclear layer was much more extensively destroyed. The ophthalmoscopic appearances during the earlier stages of the disease in some of these cases (Greenfield and Holmes, 1925) suggest that the degeneration usually commences in the foveal region and spreads outwards, although some isolated areas of degeneration may be found in the peripheral retina (Stock, 1908).

No report of the examination of the retina in a case similar to Case III has been found in the literature. The changes here were similar to those in Case I although much less severe. They might have passed unnoticed unless the PAS technique had been used; but the fuchsinophil granules in the nerve cells as well as in the large phagocytic cells were clearly seen by this technique.

This technique was also valuable in demonstrating the lipoprotein in the outer segment of the rods and cones. To what extent the intensity of staining here varies in normal retinæ has not yet been determined, but it has been present in greater or less degree in all eyes so far examined. The finer structure of this lipoprotein has recently been examined by electron microscopy, polarized light and X-ray diffraction and has been shown to be similar to that of myelin, with orientation of the lipid molecules in the long axis of the rods. The PAS technique, by oxidizing the lipid, appears to render it more insoluble by xylol, so that it remains permanent in sections mounted in xylol balsam. The method also stains the internal limiting membrane brightly, and is generally a valuable staining method for the retina.

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[*February* 1, 1951]

MEETING AT THE MAIDA VALE HOSPITAL FOR NERVOUS DISEASES, LONDON, W.9

Heredopathia Atactica Polyneuritiformis (Refsum's Syndrome).—DAVID B. CLARK, M.D. (for MACDONALD CRITCHLEY, M.D.)

A man, aged 30, born of a consanguineous marriage, complains of pains in the knees, poor vision at night, weakness and unsteadiness, and paræsthesiæ in the hands. Significant physical findings include the following: Constricted visual fields, extreme hemeralopia, small pupils fixed to light and accommodation-convergence, and non-dilatable with homatropine, cocaine, and adrenaline. Slight nystagmus on lateral gaze. Mild binaural deafness. General reduction in motor power, more marked in legs than elsewhere. Thin muscles without fasciculations. Mild distal sensory impairment in all limbs, more marked in the legs. Marked ataxia of all four limbs. Absent deep tendon reflexes and abdominal reflexes, with flexor plantar responses. Firm, non-nodular peripheral nerves. No evidence of sphincter disturbance, or story of lightning pains. Laboratory findings include: Blood and C.S.F. W.R.

persistently negative. C.S.F. total protein 200 mg.% without pleocytosis. X-ray evidence of erosion of femoral condyles, without change in joint spaces or articular cartilages. Normal E.C.G. Normal pyruvate tolerance. Bilateral high-tone deafness of perceptive type. Absence of myelinated nerve fibres, without lamellar hypertrophy of Schwann cells or amyloid deposits, in biopsy specimen of interdigital nerve of foot.

The case corresponds closely to the syndrome described by S. Refsum in 1946 (*Acta psychiat., Kbh.*, Suppl. 38) and named by him as above. It is to our knowledge the first case so diagnosed in Britain.

Multiple Angiolipomata and Hypersomnia.—HELEN DIMSDALE, M.D., F.R.C.P.

History.—S. V., male, aged 51. For two years has had attacks of hypersomnia. May occur day or night, incidence about one a month, duration two to three days. Headache and mild polyuria on waking. Disturbance of sleep rhythm, drowsy and lethargic during the day, difficulty in sleeping at night. Duration of sleep three and a half to five hours, wakes up frequently. Mildly depressed. Shaves daily. Weight decreased since onset of symptoms, with diet and Dexedrine.

Family history.—Married, 2 children. Brother, aged 44, died of a brain tumour (glioblastoma multiforme).

Past illnesses.—For the past thirty years he has had a number of subcutaneous swellings.

On examination.—Moderate obesity. No hypotrichosis. No hypogonadism. Numerous subcutaneous lipomata, about ½ in. to 2½ in. in diameter on forearms, lower abdomen, flanks and thighs. C.N.S.: Fundi normal. Fields full. Pupils moderately contracted. Left slightly larger than the right. Bilateral ptosis. Condition during attack resembles deep normal sleep, but patient is sometimes unrousable. Eyelids ptosed, and eyes turned upwards. Limbs hypotonic.

Investigations.—C.S.F. normal pressure and constituents. Blood W.R. negative. X-ray skull and chest: N.A.D. Air encephalogram: N.A.D. Third ventricle and basal cisterns appear normal. Resting E.E.G. normal. High (i.e. normal) threshold to Metrazol and photic stimulation. Record during an attack characteristic of early stages of sleep, showing well-marked "spindling".

Biopsy (Royal Free Hospital): Swelling from right arm and abdominal wall. Both are angiolipomata.

Comment.—Hypersomnia may be due to an angiolipoma in the region of the posterior hypothalamus.

Progressive Exophthalmoplegia with Muscular Atrophy, Myasthenia, and Thyrotoxicosis.—REDVERS IRONSIDE, F.R.C.P.

S. J., male, aged 54. Caterer.

Ten years' history of exhaustion, with profuse sweating at night and in hot weather; loss of 2½ stones (16 kg.) weight in past fourteen months. Fourteen months ago diplopia with variable ptosis in right eye, sometimes complete ptosis for weeks. Twelve months ago admitted to Atkinson Morley Hospital and found to have bilateral progressive external ophthalmoplegia (unresponsive to Prostigmin). Slight right facial weakness and wasting of the small muscles of right hand (Fig. 1). Fasciculation in shoulder-girdle muscles and left extensor plantar response. C.S.F., skull X-ray and E.E.G. normal (26.2.50).

FIG. 1.—To show wasting of small muscles of the hand, and dropping of the fingers (right).

Nine months ago his memory began to fail, and this was for a time associated with euphoria. Later difficulty in articulation, chewing and swallowing, dropping of lower jaw and fingers, and difficulty in elevating upper limbs.

No family history of ophthalmoplegia, muscular wasting or goitre. One son, aged 24, is mentally defective.

On examination.—No palpable thyroid enlargement. Pulse 70–90/min. Right exophthalmos with ptosis. Variable lid-retraction in left eye. All external ocular movements grossly restricted but some elevation possible. No diplopia. Pupils normal. No periocular œdema. Fundi normal. Masseters and temporals wasted, smile feeble and face expressionless in repose. Wasting and weakness of trapezii, spinati, deltoids and rhomboids, and slighter global weakness and wasting of the muscles of lower limbs, especially the dorsiflexors of feet. Occasional fasciculation in shoulder-girdle muscles. No sensory changes. All tendon reflexes elicited. Left plantar response equivocal. Abdominals present.

Blood W.R. negative. Other routine examinations normal.

Prostigmin test: 3 p.m., atropine gr. 1/100; 3.20 p.m., Prostigmin 2·5 mg. 3.30 p.m., colic; 3.35 p.m., diplopia; 4.20 p.m., marked improvement in the grips (tested by repetitive handgrips and dynamometer), in power of deltoids, extensors of fingers and iliopsoas group. Eye movements returned to 50% of normal (Fig. 2).

Patient has been given oral Prostigmin which is losing its effect.

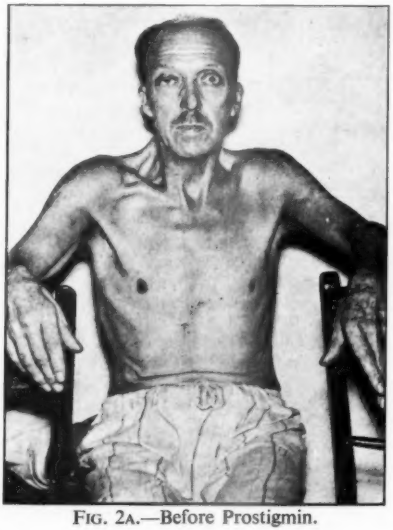

FIG. 2A.—Before Prostigmin.

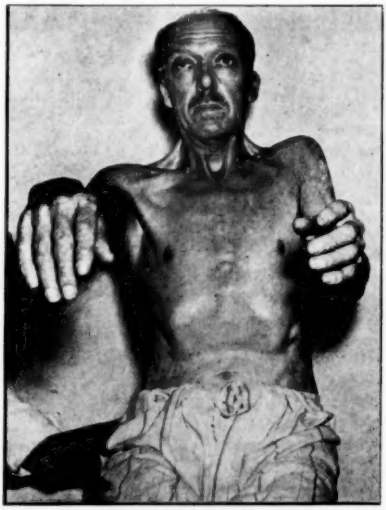

FIG. 2B.—Ten minutes after intramuscular injection of atropine gr. 1/100, Prostigmin 2·5 mg.

Radioactive iodine test, 13.1.51 (Drs. Russell Fraser and Q. J. G. Hobson):

Time	Urinary excretion of I^{131} Subject	Normal
0–8 hr.	10·6%	25–50%
8–24 ,,	1·1%	7–20%
24–48 ,,	1·1%	0–10%
Total	12·8%	
8–48 hr.	2·2%	

i.e. the excretion of radio-iodine is greatly reduced, as in thyrotoxicosis (confirmed by subsequent test).

POSTSCRIPT (July 1951).—The patient died on 9.3.51 in a state of partial respiratory paralysis.

At post-mortem (Dr. J. Vaughn, St. Bartholomew's Hospital) a few lymphocytes were seen in the calf muscles, but the external ocular muscles were microscopically normal. The thyroid gland showed no hyperplastic changes; the thymus was represented by a small residuum of fibro-fatty tissue. (Histological investigation is not yet complete.)

Angiomatous Malformation.—REDVERS IRONSIDE, F.R.C.P.

W. J., aged 56. Ticket collector.

History of recurrent bouts of left supra-orbital headaches for twelve years, always worst at night and lasting one to one and a half hours. Sometimes associated pain behind left eye and in left cheek. Shortly after onset of headaches he began to drag the right foot and this has become more marked. No history of fits or migraine.

There is a faint port-wine stain in left supra-orbital region and scattered dark blue angiomatous masses in the skin and subcutaneous tissues of left arm, neck and right thenar eminence.

When both jugular veins are compressed in the neck or when the head is lowered a mass of tortuous and dilated veins becomes evident in the left forehead and eyelids, and the left eye becomes proptosed. With the patient's head lowered, a systolic murmur can sometimes be heard over the *right* eye.

Some impairment of cutaneous sensibility over the forehead on the left side is due to alcohol injection of the supra-orbital nerve (October 1950). Slight spasticity of right leg with increased knee and ankle jerks on right side. Both plantar responses extensor. Vibration sensibility impaired over both tibiæ.

B.P. 120/80. Blood W.R. negative. Urine normal.

Plain X-ray of skull shows calcification in the posterior attachment of the falx.

Left arteriogram (Dr. David Sutton): Abnormal collection of vessels above sella; several of these are hypertrophic (Fig. 1). Large dilated veins in this region are in the early phlebogram phase.

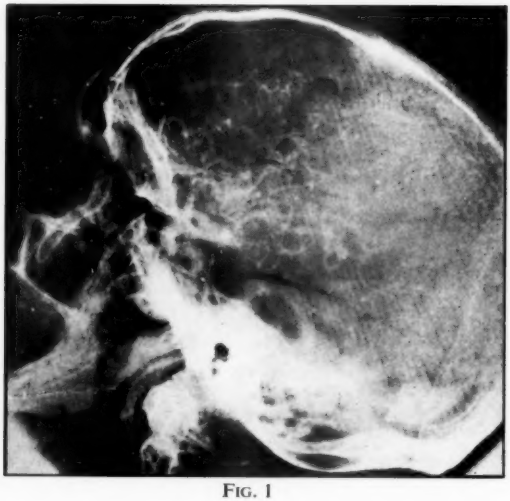

FIG. 1

Right arteriogram: Increase in calibre and tortuosity of the arterial vessels. Venous channels on the lateral surface of the hemisphere appear large in calibre.

The case is of interest in the preponderance of capillary and venous elements in the malformation.

? Disseminated Sclerosis and Angioneurotic Œdema.—NIGEL COMPSTON, M.D., M.R.C.P.

A. H. B., male, aged 31, was admitted to the Middlesex Hospital on 18.9.50 on account of progressive right-sided hemiplegia. He denied the presence of any neurological or allergic symptoms at any time before November 1942.

History.—In November 1942, aged 23, whilst serving in the Sudan, developed sandfly fever. During convalescence, three weeks later, he developed severe urticaria and angioneurotic œdema. As the tongue was swollen, arrangements were made to transfer the patient to hospital, but during the journey the condition settled down spontaneously. Within two weeks of this episode the patient noticed weakness of all limbs, at first particularly the right arm and a little later the right leg. He was readmitted to a military hospital, where a lumbar

puncture was performed, and although he was not told the diagnosis he was boarded home to the United Kingdom, where he was discharged from the Service. Since then the patient has noticed progressive loss of power of the right arm and leg. Since May 1945 there has been persistent impotence, since November 1947 urgency and frequency of micturition with occasional incontinence, and since 1948 paræsthesiæ and numbness of the right arm and leg. During this period he has had recurrent attacks of angioneurotic œdema, and states that during such attacks his ability to walk is markedly affected. During attacks he is limited to less than 100 yards, whilst at other times he can manage more than a quarter of a mile. The effect of angioneurotic œdema has been invariable.

Examination on admission revealed normal mood and intellect, and apart from the presence of generalized dental sepsis all systems other than the central nervous system were found to be normal.

Central nervous system.—Pallor of both optic discs. Visual acuity, corrected R. 6/9, L. 6/18. Centrocæcal scotoma to 3/2,000 red left eye. No nystagmus. Arms: power impaired right, normal left. Tone normal. No ataxia. All reflexes increased, right more than left, but right triceps jerk inverted. Impaired perception of pin-prick, hot and cold, and cotton-wool right hand. Abdominal reflexes depressed. Legs: moderately severe paresis right, slight left. Tone increased right more than left, with increased reflexes and bilateral extensor plantar responses. Impaired vibration sensation both feet, postural sense normal. Impaired perception of pin-prick, cotton-wool, and hot and cold over right foot.

Investigations.—C.S.F.: cells 1 per c.mm., protein 70 mg.%, Pandy test positive, W.R. 00000, Lange curve 0221100000. Blood W.R. negative. Skin sensitivity tests: strong positive to egg protein.

Progress.—On 28.9.50 patient developed severe urticaria which he attributed to having eaten eggs. This lasted twenty-four hours, during which time his disability was markedly increased, but it rapidly returned to normal as the urticaria faded. There was a further attack of urticaria on 4.10.50, when examination showed a marked increase in the degree of paresis and the appearance of an incomplete sensory level to pin-prick at D4 and to vibration sensation at D6.

Dental extraction, which had been recommended by the dental surgeon, was commenced under penicillin cover on 20.10.50. There was a further attack of urticaria on 4.11.50 and again during this there was a well-marked increase in the degree of disability with severe impairment of bladder function. During a further attack of urticaria on 8.11.50 examination of the C.S.F. showed 2 cells per c.mm., 60 mg.% protein and a Lange curve 0233221000. Penicillin was given for further dental extractions on 18.11.50, and nine days later the patient became markedly feverish with severe joint pains and again generalized urticaria and angio-neurotic œdema. During this attack, which lasted for seventy-two hours, there was complete loss of all forms of sensation below the level of D4, over-reaction to cutaneous stimuli just above this level and almost complete loss of power in the right leg. Examination of C.S.F. showed 5 cells per c.mm., 30 mg.% protein, and a Lange curve of 2334321000.

Since the completion of dental extraction and on an egg-free diet there have been no further attacks of urticaria, and the patient's neurological disability has decreased, although he still shows a persistent paresis of the right leg with about 30–40% loss of power.

Comment.—Foster Kennedy (1950) has recently criticized the diagnosis of disseminated sclerosis in those cases that follow a favourable course. He considers that many of these cases are due to allergic manifestations in the central nervous system of a benign nature. He states: "Far more cases of *allergic* [*sic*] retrobulbar neuritis take place than occur as an early sign of multiple sclerosis." Foster Kennedy describes cases showing recurrent myelitic symptoms which he considers allergic in origin. The present case might be held to differ in that it has not run a benign course, there being considerable disability when active allergic manifestations are not present. If there were no history of urticaria in this case it would be difficult to arrive at any diagnosis other than that of disseminated sclerosis. It may be, therefore, that in this case the lesions in the central nervous system are those of disseminated sclerosis, and that their degree of activity is affected by the patient's allergic condition. Autopsy in this type of case would be most informative.

I am grateful to Dr. D. McAlpine for permission to report this case.

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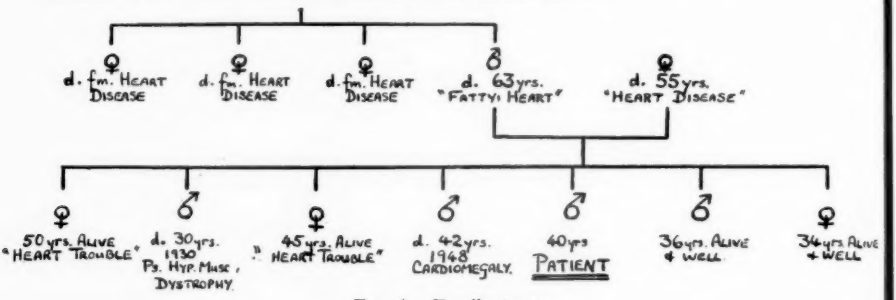
POSTSCRIPT (July 1951):—Since this case was reported, although the patient has remained free from urticaria, there has been a further marked increase in the degree of paralysis.

Pseudohypertrophic Muscular Dystrophy with Cardiomegaly.—L. G. KILOH, M.D., M.R.C.P., and S. NEVIN, M.D., F.R.C.P.

G. C., male, aged 40, noticed enlargement and hardness of calf muscles at the age of 10 years. Although slower than other boys. no definite weakness of legs until 16 years old and this only became severe at 25 years of age, by which time his thighs showed definite wasting. Weakness of upper arms noticed at the age of 20 and had become severe and accompanied by obvious wasting by the time he was 32.

May 1950: Breathlessness on exertion which became progressively worse.

August 1950: Admitted to hospital in severe cardiac failure.


d. fm. Heart Disease
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d. 63 yrs. "Fatty Heart"
d. 55 yrs. "Heart Disease"
50 yrs. Alive "Heart Trouble"
d. 30 yrs. 1930 Ps. Hyp. Musc. Dystrophy
45 yrs. Alive "Heart Trouble"
d. 42 yrs. 1948 Cardiomegaly
40 yrs PATIENT
36 yrs. Alive & well
34 yrs. Alive & well

FIG. 1.—Family tree.

On examination.—Cranial nerves normal. Gross symmetrical wasting and weakness of muscles of shoulder girdles, upper arms, spine, pelvic girdles and thighs. There is pseudo-hypertrophy of forearm and calf muscles. The biceps, triceps, supinator and knee-jerks are absent but both ankle-jerks are present. Plantars flexor. No sensory changes.

When first seen (4.10.49) apex beat 4 in. in fifth space. Harsh late systolic murmur to left of sternum. *Screening*: globular heart, enlarged in all diameters.

On admission (4.8.50): very dyspnœic; œdema of lumbar region and ankles. Jugular veins engorged; liver 2 in. below the costal margin and tender. Pulse 130/min., multiple extrasystoles. Apex beat 5 in. in fifth space. Harsh late systolic murmur to left of sternum. Presystolic gallop rhythm. Blood pressure 110/90. Signs of small effusion at right base.

X-ray of chest: considerable enlargement of heart, pulmonary congestion and right basal effusion.

E.C.G.: Left bundle branch block.

Rapid response to routine treatment of cardiac failure, heart size reduced, though not to its former limits.

No valvular lesion or hypertension present to account for cardiomegaly. It is likely that it, too, is myopathic in nature. The fact that one of the patient's brothers died with cardiomegaly (*see* Fig. 1) but without obvious dystrophy of his voluntary muscles, raises the interesting question as to whether muscular dystrophy can give rise to isolated affection of the heart.

Myotonia Congenita.—P. H. SANDIFER, F.R.C.P.

S. A., aged 13.

Since birth the child has been stiff in all her movements; she did not kick her legs much as a baby and when walking began at 15 months she was stiff, awkward and unable to get up if she fell. At the age of 11 slight improvement began but myotonia persists. Muscles of the shoulder-girdle have always been bulky but not noticeably weak. Legs weak in climbing stairs, yet was able to play games at school. At 10 years her feet began to turn in and corrective operations were later performed.

Past history.—Birth injury to foot and had to wear a splint for twelve months.

Family history.—Father, father's brother, mother, a maternal aunt and maternal grandmother all presumably affected. Patient's sister, aged 8, is well. No familial pes cavus deformity.

On examination.—Myotonia of masseters, tongue and limbs. Hypertrophy of shoulder-girdle muscles, spinal group and thighs. Atrophy of forearms with marked hollowing of palms of hands. Bilateral knock-knee and club-foot deformity.

Muscle biopsy.—Dr. W. H. McMenemey reported as follows: The main features noted were: (1) variation in diameter of individual muscle fibres from 7–135 μ; (2) some loss of striation; (3) an increase in nuclei, confined, however, to a minority of the fibres, with occasional instances of "migration" of nuclei into the sarcoplasm; and (4) slight fat replacement and increase in fibrous connective tissue.

Section of Obstetrics and Gynæcology

President—V. B. GREEN-ARMYTAGE, F.R.C.O.G., M.D., F.R.C.P.

[*March* 16, 1951]

Uterine Contractility and Cervical Dilatation

By S. R. M. REYNOLDS, Ph.D., D.Sc.

Department of Embryology, Carnegie Institution of Washington, Baltimore 5, Md., U.S.A.

IN outlining the subject of abnormal uterine action in labour, I must do it from the standpoint of the physiologist rather than that of the clinician.

The immediate problem which confronts the uterus at the end of gestation is that of dilating a closed cervix. During pregnancy, the uterus develops sufficient latent power to overcome at a definite future time a definite resistance against which it does not test its strength until the moment of conflict arrives. Cervical resistance involves in the first phase the resistance of the tissues of the cervix to passive stretching but there may be additional resistance arising from a nervous action which, in my opinion, has yet to be defined. Cervical resistance likewise involves inherent individual differences related to uterine growth processes and to previous obstetrical history, particularly parity.

What is the magnitude of the force necessary to cause cervical dilatation? Recent studies in which pressures within the amniotic sac were measured (Alvarez, Caldeyro and Reynolds, 1950) show that when labour proceeds at a normal rate, the absolute pressure developed in the uterus during uterine systole is in excess of 24 mm. mercury, usually between 30 and 70. If uterine systole averages between 16 and 24 mm. mercury, the progress of labour is slow; labour is delayed or prolonged. When, however, this pressure is less than 16 mm. of mercury, the cervix does not dilate. The condition then may be one of false or prodromal labour or of inertia. Admittedly these conclusions are tentative pending more detailed studies. Such studies will recognize the role of parity, fœtal position, uterine load, uterine hypoplasia and the like. The figures mentioned do give us the range of our problem, however. How, one asks, does the uterus achieve the minimum average force necessary to overcome the resisting cervix?

PHYSIOLOGICAL BASES OF CERVICAL DILATATION

There are three basic mechanisms by which a pattern of uterine contractions is achieved which is capable of dilating the cervix. These are morphological, physical (biophysical), and biochemical mechanisms.

The morphological mechanism is concerned with uterine growth processes during pregnancy. There is not time to recount these here, but they have been described recently in another place (Reynolds, 1949). The result of the normal growth processes is to effect in the human uterus at term an advantageous distribution of muscular tissue. The fundus is double the thickness of the cervix and lower uterine segment prior to the beginning of effacement. There is, therefore, a preponderance of contractile power in the fundus.

The power which a muscle can develop is directly proportional to its thickness. This, then, is a first requisite of normal labour yet it is one which uterine hypoplasia or over-distension may negate. The role of such factors as obstetrical faults is not really known.

The physical basis of normal labour is concerned with the relative difference in tissue tension between the opposite ends of the uterus, in the fundus and cervix respectively. The Reverend Samuel Haughton, M.D., was the first to describe this in 1873 (Haughton, 1873) although it is only within the past two years that his views have been recognized (Reynolds, 1949).

Haughton has shown that since tension in the tissues of a hollow organ is a function of the pressure within and the principal radii of curvature, the relative tensions in different regions of the uterus may be judged by knowing the radii of curvature in different parts. With respect to the fundus and the cervix, total tension in the tissues of the fundus is about double that in the cervix.

I need not here elaborate the significance of this conclusion. The effect of increasing the initial load or tension on a muscle, whether cardiac, striated or smooth, is to increase the contractile power of that muscle. We see, therefore, that Nature has deployed its greatest tension in that part of the uterus which is also thickest. For these two reasons, then, the action of the uterus in labour normally will be most powerful in the fundus.

The biochemical basis of uterine action in labour is a long, new, and most important part of the story of uterine action in labour. I must limit my remarks briefly to but one aspect of the subject.

The active contractile protein of muscle, called actomyosin, can be isolated from the living cell and its concentration and quality determined. When uterine muscle at term is so analysed, it is found (*see* Fig. 1) that the actomyosin is far more contractile than actomyosin from the non-pregnant uterus and far more contractile than that obtainable from uteri taken after irradiation menopause. Uterine actomyosin at term approaches in quality that of striated muscle (Csapo, 1948, 1950). Moreover, the concentration is far greater at term than it is in the non-pregnant uterus, but *only* in the fundus. Since actomyosin molecules are the "fingers" which do this work, it is clear that Nature places a metabolic advantage in the fundus for doing muscular work at term. We witness here a unique combination of morphology, biophysics and biochemistry working together to put greater contractile power in the fundus than elsewhere. Clearly, *fundal dominance* should be one of the outstanding features of the pattern of uterine contractility in labour. Is it?

Pattern of Uterine Contractility in Normal Labour

The only way which I know to analyse the patterns of uterine contractility is to record contractions from three or more points simultaneously. This we began to do in 1947, with the result shown in Fig. 2. A multichannel tokodynamometer was developed which recorded by three sensitive electric fingers (strain gauges) the differences in pressure between the centre and the circumference of each of the three rings (Reynolds, Hellman and Bruns, 1948). Since each unit is set to the same sensitivity, differences in intensity, frequency, duration, rhythm and other aspects of contractility in different regions of the uterus can be measured.

A sample of two contractions from a normal labour is shown in Fig. 3. Here we see the evidence of fundal dominance as the uterus itself writes it. The contractions are stronger and longer in the fundus than lower down in the uterus. There is a gradient of diminishing contractility from above, downward. This is a fundamental characteristic of all good labours. It will be noted that this pattern may be seen before labour, during Braxton-Hicks contractions, and in some cases of prodromal labour. The fact remains, however, that labours do *not* progress well without this pattern.

When data from 151 women were compiled and analysed by business punch card sorting machines, the average characteristics of normal, uncomplicated labours were determined (Hellman, Harris and Reynolds, 1950). The simplest summary of this is shown by the curves of Fig. 4. Here, work done by the fundus, mid-uterus, and the lower uterine segment in each third of the first stage of labour is shown, along with the curve of cervical dilatation and the frequency of contractions. How well the morphological, biophysical and biochemical factors are combined in the fundus to achieve their destined purpose!

The difference between the work done by the multiparous and the primiparous uterus in the first stage of labour is shown in Fig. 5. The basis of this difference is not known for a certainty. We may surmise, no doubt, that it is the result of improved fundal action in the face of less resistance to be overcome in multiparous women by uterine contractions after the cervix is dilated to 5 cm.

Patterns of Contractility in Abnormal Labour

One of the paramount problems in obstetrics arises when normal mechanics fail, and abnormal labour supervenes. The term "abnormal labour" is a clinical term, and requires definition. In the obstetrical clinic at Johns Hopkins Hospital, the definitions used and on which our work is based are as follows:

Normal labour begins when the cervix is 2 cm. dilated and it continues to full dilatation within fourteen hours in the case of primiparous, and eight hours in multiparous patients.

Prodromal labour is characterized by continued intermittent pain associated with uterine contractions at term without cervical dilatation but the pains continue into those of normal labour.

False labour is the same as prodromal labour, except that the pains subside before the cervical dilatation of labour begins.

Delayed labour is the result of cessation in the progress of cervical dilatation for more than one hour.

Prolonged labour results when full dilatation is not achieved until after fourteen hours in primiparous and eight hours in multiparous patients.

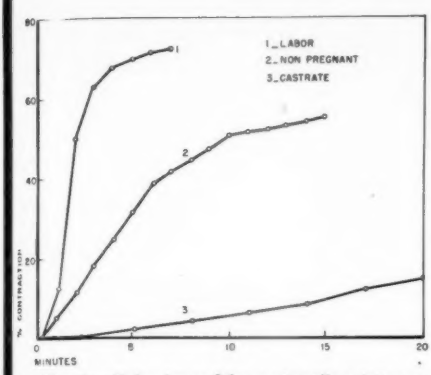

FIG. 1.—Behaviour of the contractile substance of the myometrium (actomyosin) when obtained under different hormonal conditions. Csapo (1950) modified from *Nature*.

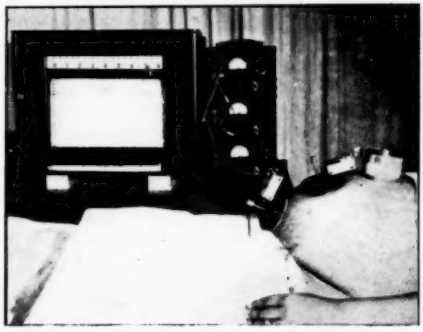

FIG. 2.—Picture of three "electric fingers" (strain gauges) in place on the abdomen of a woman in labour. A three-channel tokodynamometer (Figs. 2 and 3: Reynolds, 1951; courtesy of *Amer. J. Obstet. Gynec.*).

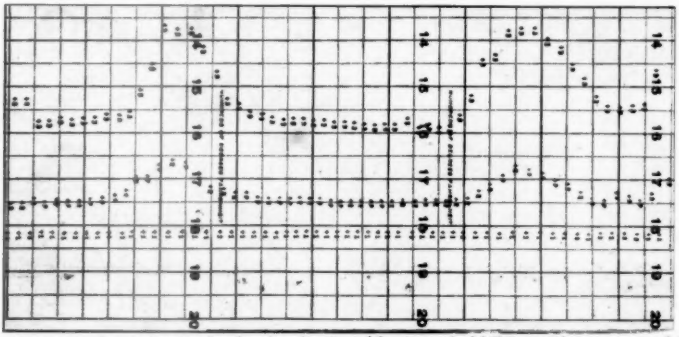

FIG. 3.—Record of activity in the fundus (top), mid-uterus (middle) and lower part of the uterus (bottom) during labour. Two contractions. Note contraction form, fundal dominance and inactive lower uterus. Vertical lines at 20-second intervals. Horizontal lines = 50 g. force on strain gauge.

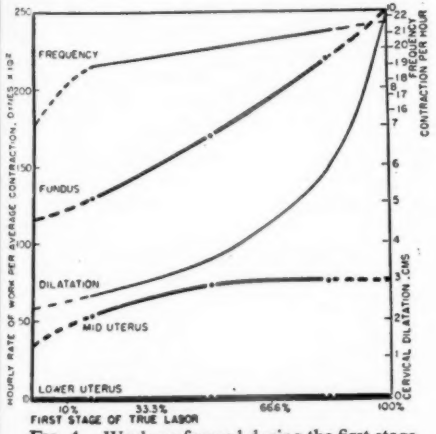

FIG. 4.—Work performed during the first stage of labour by the fundus, mid-uterus, and lower part of uterus. Based on 677 twenty-minute periods of observation in 151 normal women with uncomplicated labours.

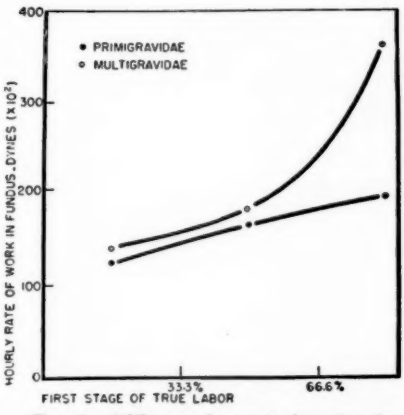

FIG. 5.—Difference in work done by the fundus in primiparous and multiparous women in the first stage of labour (Figs. 4 and 5: Hellman, Harris and Reynolds, 1950; courtesy of *Bull. Johns Hopk. Hosp.*).

Uterine inertia results when labour has been prolonged for more than twenty-four hours. These definitions may be debatable, but within their limitations we have made numerous observations in each of these categories. I shall show you records from only a few, however, for the fundamental faults appear to be rather similar in all, the result depending merely upon *when*—before or during labour—the conditions giving rise to them develop. *Why* they develop is quite another matter. Most often, when abnormal uterine action occurs it is characterized by inco-ordination with too little pressure developing within the uterus to overcome the resisting cervix. These conditions are shown by the following examples, taken from a recent collaborative study which I had an opportunity to make with Professors Alvarez and Caldeyro in Montevideo (Alvarez, Caldeyro and Reynolds, 1950). We used internal (amniotic sac pressure) and seven-point external tokography simultaneously.

Normal labour (Fig. 6).—This record is shown because although the record came from a patient in clinically normal labour, we see, with seven-point recording, that co-ordination of

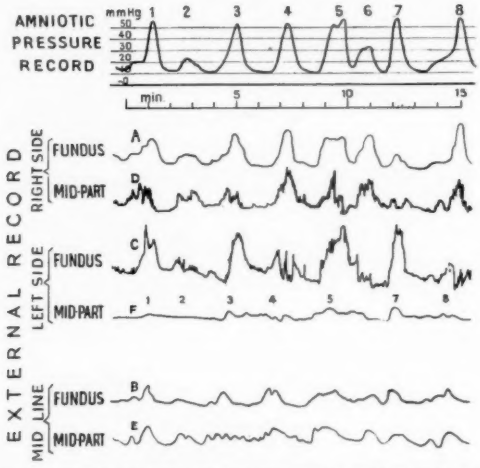

FIG. 6.—Simultaneous recording of intra-uterine pressure (amniotic sac) and six-channel external tokography. Section of record from *normal labour*. Note fundal dominance, synchronism, intensity of contraction, and pressure in the uterus well over 24 mm.Hg during uterine systole. Note two contractions (Nos. 5 and 6) in which there is asynchronism. There is right-sided dominance in contractions Nos. 2, 4, 6 and 8; left-sided dominance in contractions Nos. 1, 3, 5 and 7. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surgery. Gynec. Obstet.*

uterine action is not perfect. Even so the absolute intra-uterine pressure is characteristic of good labour, averaging 38 mm. mercury during uterine systole. There is good fundal dominance on the right and left sides, but this is not so noticeable in the mid-line. There is good synchronization of different parts of the uterus except in the case of contraction numbers 5 and 6. There is some irregularity in rhythm, intensity and form. The right side predominates in contractions 2, 4, 6 and 8. The left side predominates in contractions 1, 3, 5 and 7. In normal labour, therefore, we observe a small proportion of contractions which are not completely co-ordinate. Enough are sufficiently co-ordinated, however, to effect cervical dilatation.

Prolonged labour is demonstrated by the portion of record shown in Fig. 7. This was obtained in a 39-year-old patient, gravida iv, para. iii. The first stage of labour lasted about eighteen hours. The intensity of intra-uterine pressure during uterine systole, averaging only 15 mm.Hg, was insufficient for rapid cervical dilatation. There was fundal dominance on the right side but not on the left. The lower part of the uterus gave evidence of contractility, while normally it is inactive. There was marked asynchronism between three regions of the uterus, which contracted independently of each other. These were: (1) each side of the fundus, (2) the mid-uterus on the left side, and (3) the lower right side of the uterus. There were marked irregularities in rhythm, intensity, and shape of the contractions. Much of the time, the amniotic pressure did not descend during uterine diastole to the normal level of 10 mm.Hg. Although, therefore, the contractions were weak, there was what would be called "hypertonia", but actually, the pressure was sustained by virtue of pressure exerted by the continuous effect of local and weak contractions in different parts of the uterus.

False labour, as shown in Fig. 8, is one of several general patterns of contractility which we have seen in this condition. The absolute intensity of pressure during uterine diastole in the uterus is low, averaging 9 mm.Hg. There is absence of fundal dominance because the contractions in the mid-uterus are stronger than those of the fundus. There is good synchronization of activity between the several parts of the uterus. Between contractions, the pressure descends to lower than normal levels, substantially *less* than 10 mm. mercury because the patient is not in labour. There is regularity in the rhythm of the contractions, but an irregularity in intensity which increased and decreased periodically throughout the period of observation.

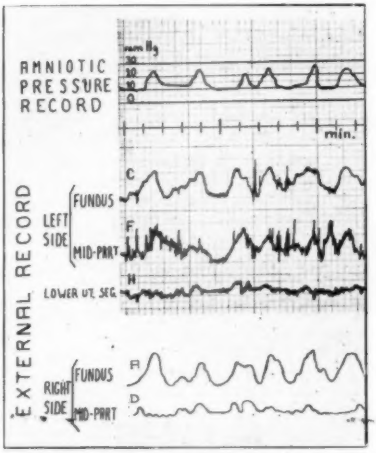

FIG. 7.—Simultaneous internal and external tokography in a case of *prolonged labour*. *See text* for analysis. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surg. Gynec. Obstet.*

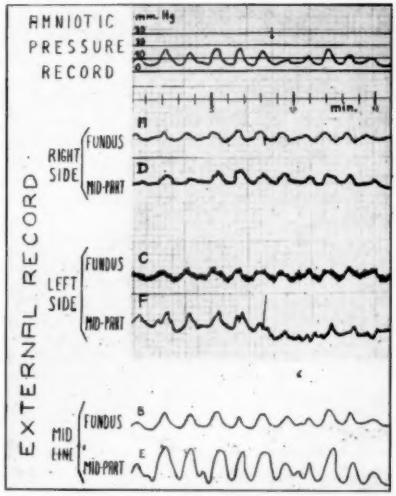

FIG. 8.—Simultaneous internal and external tokography in a case of *false labour*. *See text* for analysis. Alvarez, Caldeyro and Reynolds (1950). Courtesy of *Surg. Gynec. Obstet.*, **91**, 644 and 645.

More examples of these conditions, along with other abnormal types of labour, might be cited. However, we may summarize on the basis of what I have presented here what might be said of the whole. We have never seen a constriction ring, except as it develops intermittently during uterine contractions. With so-called "wooden" uterus in premature separation of the placenta, there is a sustained, high, intra-uterine pressure, but it is still associated with *rhythmic* activity in localized regions of the uterus without fundal dominance. In one case, this was seen in the mid-region of the uterus only, as strong rhythmic contractions continued at the top and bottom of the uterus. With onset of cervical dilatation, however, a well co-ordinated gradient of contractions was seen. In a few cases of false labour reverse gradients have been seen.

The characteristics of contractility which typify a normal labour may be briefly summarized by saying that there is normally good synchronization between different parts of the uterus with good fundal dominance. One side of the uterus may contract more strongly than the opposite side. When this is marked, or when the asynchronism is especially marked between the fundus, mid-uterus, and lower part of the uterus, the labour may be abnormal, *depending upon the degree to which asynchronism dominates the situation.* We may note that amniotic pressure sufficient to dilate the cervix is, in any moment, the sum of the pressures developed by the different contractions of the several parts of the uterus. This is influenced by two factors, namely, (1) the intensity of this activity at any one point, and (2) the synchronization of activity between the several contracting parts. The cervix dilates well *when the three characteristics of good contractility*, namely, (1) *good synchronization*, (2) *good fundal dominance*, and (3) *contractions of sufficient intensity*, are present. In normal labour these characteristics are seldom present all the time. When the deviation is marked and persistent, the labour becomes, clinically, abnormal, and the type of clinical characterization depends upon *when* the deviation begins with relation to the beginning of true labour.

We do not know why normal conditions do not always prevail. Factors of uterine growth, of physical forces, and uterine metabolism remain to be explored in relation to recent knowledge of the behaviour of the uterus in labour. I will mention but two points, in order to indicate promising avenues of investigation.

In the first place, my recent colleagues, Drs. J. S. Harris and I. H. Kaiser, have found that of all substances known to effect the contractility of the human uterus, epinephrine and nor-epinephrine are most potent. If these are given by intravenous drip at rates which could not possibly raise their concentration by as much as one-thousandth of a microgram, the normal patterns of contractility of the uterus in late pregnancy or in labour are destroyed. Epinephrine reduces or abolishes uterine contractility and nor-epinephrine raises tone (Kaiser, 1951; Kaiser and Harris, 1950). It is tempting to speculate that one or both of these substances may be secreted into the blood stream as a result of the pains of labour, especially in those women who are tense, or fearful of labour. While there is evidence that both substances are secreted under some conditions of stress, we do not know what the situation regarding this possibility is during labour. My colleague, Dr. Ramon Garcia, is at present engaged in such a study. In time we may know what fluctuations occur in blood epinephrine levels during normal and abnormal labours.

A record which was obtained on a hypnotized patient is shown in Fig. 9. This record was obtained last April on the service of Professor Rodriguez-Lopez of the Pereira Rossel

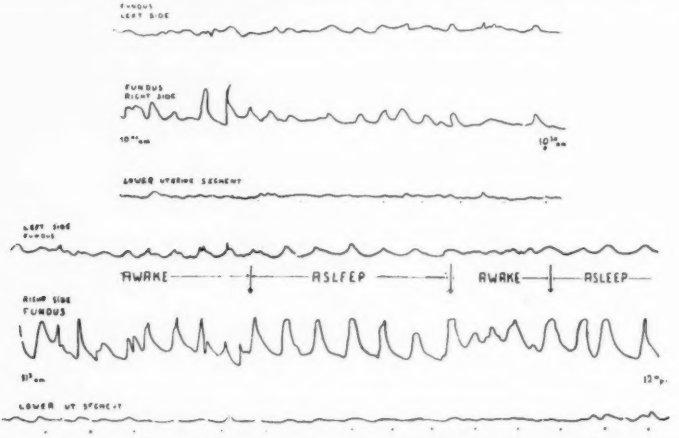

FIG. 9.—Record of the effect of induction of hypnotic sleep twice during a half-hour record in the first stage of labour (*see text*). Right-sided dystocia persisted, but the form, rhythm and intensity changed.

Hospital in Montevideo. During pregnancy, the suggestion had been made to the patient when under hypnosis that she would not experience pain in labour. Early in labour, while awake, her uterus exhibited weak, irregular contractions on the right side. The remainder of the uterus was inactive. Within an hour, the patient's cervix was found to be dilated to 5 cm. At this time, the early, right-sided activity was very strong and somewhat irregular as to form. The patient was then put in a state of deep hypnotic sleep, which I myself can testify was most effective. The rhythm and amplitude of contractions became remarkably regular in form and rhythm. The right-sided dystocia persisted, however. Even so, the cervix was dilated to 7 cm. within thirty minutes. On temporarily awaking, the earlier irregular pattern of contractility returned, but it improved promptly a second time during a second period of sleep. The record had to be terminated when, on palpation, the membranes ruptured and reflex bearing down movements became extreme. The cervix was now fully dilated. At no time did the patient have pain, except upon bearing down, when there was deep pain over the promontory of the sacrum.

What is the meaning of this observation on the effect of hypnotic sleep? I suspect that when more is known about this condition, we will discover what every obstetrician knows. We will find that sedation, analgesia, hypnosis, or psychological subordination such as may be achieved in so-called natural childbirth have one thing in common. They spare the uterus the physiological insult and consequence of painful stimuli in the organism, and these painful stimuli are, of course, an inevitable concomitant of the process of cervical dilatation during labour.

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Professor A. St. G. Huggett: Dr. Reynolds has put the results of his own work on pressure measurements and changes within the uterus: he has presented the relation between muscular structure and the tensile forces developed at different stages and, in addition, has outlined the possible application of the work of Szent-Gyorgi on actomyosin to this problem. Finally, he has shown the results of studies of the human uterus as illustrating the general principles he has outlined.

I will discuss certain physiological problems bearing on uterine contractility which await solution by the clinician and the laboratory worker.

Enlargement of the uterus during pregnancy.—The outstanding point about the uterus and its contents which distinguishes them from the other organs of the body is the time factor. The rate of change or the rate of growth, both in regard to the myometrium and the contents, is stupendous when compared with any other organ or the normal growth of the body. So far very little has been done to study the factors concerned in the muscular hypertrophy. The muscle fibres enlarge from lengths of 50μ to from 200 to 600μ in length; that is, a single nucleated cell lengthens to more than half a millimetre, visible to the naked eye. This occurs in a period of less than nine months.

We know that the enlargement is impossible in a spayed animal but can be maintained after double ovariectomy in the latter half of pregnancy in the human and in certain animals. Here the evidence shows that the œstrogen-progesterone complex of the ovaries is replaced by placental secretion of œstrogens, progesterone and chorionic gonadotrophin. We owe to the late Professor Newton (1949) the clear outline of the control of the extra-uterine metabolism of pregnancy by the placenta as a ductless gland, and to his colleague Dewar (1950), the importance of the progesterone secretion in this respect.

Nitrogen retention.—Young (1944, 1948) has shown how the growth hormone of the anterior lobe of the pituitary is probably identical with the diabetogenic hormone of the same organ. Over-action of the anterior pituitary results in growth distinguished by nitrogen retention and deposition accompanied by hypertrophy of the pancreatic islet tissue and insulin production, but if the islets fail to respond there is an excessive liberation of glucose with diabetes. In pregnancy there is what can best be described as unstable carbohydrate metabolism, glycosuria being easily produced on giving sugar. The hypertrophy of the pituitary would appear to be an essential for the retention of nitrogen and, presumably, for the formation of uterine muscle. It is clearly of importance for the factors concerned in good uterine development to be disentangled.

Response to hormones.—Since the reactions of the myometrium to œstrogens, to progesterone and to pituitrin are capable of great variation from species to species, and also at different phases of the œstrual or menstrual cycles, they are of importance in the proper understanding of the changes in pregnancy. From the point of view of the obstetrician a matter of considerable importance is the increase in sensitivity to pituitrin, a change which in the rabbit appears to depend upon the presence of progesterone.

In this connexion one is reminded of the classical experiment of Dale and Kellaway (1921) upon anaphylaxis. They showed that in a female guinea-pig made anaphylactic to a foreign protein, the uterus when excised was thrown into violent contraction in a water-bath when antigen was added to the bath. In other words, in the prolonged period between the first and last dose the antibodies formed had passed into the uterus.

Biochemical mechanisms of the myometrium.—It is clear, therefore, that to understand the mechanisms which are responsible for the growth of the myometrium in pregnancy and for the response of muscle, we need to evaluate the factors concerned in tissue growth and, secondly, to study the dynamic action of mass enzyme systems present in the uterine musculature and their response to hormonal influences. In invoking actomyosin, Dr. Reynolds has made a start. Perhaps Dr. Dorothy Needham will enlarge on this aspect of the subject.

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Dorothy M. Needham, Sc.D., F.R.S. (*Biochemical Laboratory, Cambridge*): To the biochemist the question of uterine contractility is interesting from several points of view. Let us consider first the proteins. It has to be remembered that, in the general theories of muscle contraction, the part played by actin and actomyosin is still obscure. We can feel certain that the fibrils of muscle consist mainly of polypeptide chains of the protein myosin, arranged with their long axes parallel to the fibril axis, and X-ray photographs indicate that actin is also incorporated in this regular molecular array. But we do not know how the myosin and actin interact *in vivo*; we do not even know whether actomyosin is present as such in the muscle before contraction, as postulated by Szent-Györgyi (1948), or whether the two proteins exist together in the resting muscle, only entering into combination on contraction, as suggested by Astbury (1950). It is therefore important to get this confirmation of the significance of actin from the study of the uterus, where the physiological change in the muscle to the more active state is marked by an increase in the proportion of actin present.

Again for the biochemist, the effect of œstrogen injections upon the uterine muscle of ovariectomized animals—the rapid increase in the amount of actomyosin + myosin present and the especially dramatic increase in the adenosinetriphosphatase (ATPase) activity (Csapo, 1950*a*)—open interesting possibilities. A comparatively simple hypothesis of the mechanism of action of the œstrogen upon the protein composition of the organ would be to suppose that the non-gravid uterus contains building stones in the shape of special proteins of much smaller molecular weight which, upon the appropriate stimulus, can be readily fitted together to form the contractile proteins themselves. Such a hypothesis would include an explanation for the great rise in ATPase activity while the actomysin + myosin has only risen slightly; it is true that normally the ATPase activity of muscle seems to reside in its myosin and that in general any changes in the myosin molecule, such as those which prevent its combination with actin, prevent also ATPase activity. It is, however, known that myosin can be broken down by careful treatment with trypsin (Perry, 1951) to a state where the molecules still show ATPase activity, but have become too small to show the characteristic effects of thread formation or increase in viscosity on mixing with actin. We may have here in the uterus reacting to œstrogen an example of the opposite case—the myosin molecules building up and passing through this same stage where ATPase activity is marked but possibility of actomyosin formation is restricted. It may be mentioned that skeletal and cardiac muscle contain a protein, tropomyosin (Bailey, 1948), present to the extent of about 2·5% of the total protein, of amino-acid composition similar in many respects to that of myosin, but of only about one-tenth the molecular weight. Bailey has made the suggestion that tropomyosin may be one of the units from which myosin is elaborated.

A consideration of Csapo's figures (Csapo, 1950*b*) shows that the actomyosin + myosin content of the uterus, even when gravid, is very low compared to skeletal muscle: only about one-quarter. Thus while in skeletal muscle actomyosin + myosin makes up about 66% of the protein, in uterus it is only about 20%. One would like very much to know something about the rest of the protein in the uterus; one might look, as I have suggested, for precursors of myosin and actin.

When we turn to the energy-providing metabolism of the uterus, we find that the information all points to the course of metabolism being similar to that in skeletal muscle, but the provision of energy-rich phosphate compounds is much less than in skeletal muscle—only one-tenth to one-twentieth even in the gravid uterus (Csapo, 1950*c*; Walaas and Walaas, 1950*a*). There is some evidence that in the uterus of ovariectomized rats, the injection of œstrogen leads to a slight but significant increase in ATP and creatinephosphate content; and also (from studies making use of radio-active P) that there is increased turnover of acid-soluble P compounds after œstrogen in uterus muscle but not in skeletal muscle (Walaas and Walaas, 1950*b*).

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JOINT MEETING No. 1

Section of Obstetrics and Gynæcology with Section of Radiology

Chairman—V. B. GREEN-ARMYTAGE, F.R.C.O.G., M.D., F.R.C.P.
(President of the Section of Obstetrics and Gynæcology)

[*February* 16, 1951]

JOINT DISCUSSION ON X-RAYS AND THEIR VALUE IN THE LOCALIZATION OF THE PLACENTA

Dr. Frank Reid (*Radiologist, Harrogate and Ripon Group of Hospitals; formerly of Radcliffe Infirmary, Oxford*): *X-Rays and Their Value in the Diagnosis of Placenta Prævia.*[1]—Discussions between obstetricians and radiologists on the value of X-rays in pregnancy are usually concerned with the bony structure of the fœtus and the maternal pelvis, but I shall deal only with the radiography of the soft tissues in pregnancy, and, in particular, with the diagnosis of placenta prævia.

METHODS OF INVESTIGATION

Amniography.—This was first described in 1930, by Menees, Miller and Holly. After injecting strontium iodide into the uterine cavity to increase the radiopacity of the liquor, they were able to identify the placenta as a soft tissue shadow of lesser density by its characteristic shape.

Cystography.—In 1934, Ude, Weum and Urner originated this method, in which they estimated the thickness of the anterior wall of the lower segment, following the injection of contrast medium into the bladder.

Air inflation of the rectum.—Sohrne (1942) found cystography reliable only where the placenta prævia was wholly or partly anterior. He therefore used a combined procedure, injecting air into both bladder and rectum, in order to assess the thickness of the anterior and posterior walls of the lower segment.

Tomography.—Lloyd and Samuel (1941) described the tomographic appearances of 5 cases, 3 of which showed evidence of placenta prævia, and 2 of normal implantation. Their findings were subsequently confirmed clinically.

Intravenous placentography.—Using thorium dioxide, in animal experiments, Ehrhardt (1932) was able to demonstrate the placental site, owing to retention of the contrast medium by the reticulo-endothelial cells. In 1939 he tried the phenyl and ethyl esters of tri-iodostearic acid, but considered that neither of these substances was safe enough for the examination of patients.

PLAIN FILMS

(1) *The situation of the placental shadow.*—Snow and Powell (1934) considered that a crescentic thickening of the peripheral soft tissues, usually visible in lateral views of the abdomen, indicated the site of implantation. Figs. 1 and 2 are typical examples of the appearances usually encountered. The crescentic soft tissue shadow represents a cross-section which includes placenta, uterine muscle, and a variable amount of liquor amnii.

Dippel and Brown (1940), and many other American authors, diagnose placenta prævia when all or most of the placental shadow is on the lower half of the anterior or posterior wall, the presumption being that implantation extends well down on the invisible pelvic part of the lower segment.

[1]This work has been done with the assistance of a Leverhulme Scholarship, awarded by the Royal College of Obstetricians and Gynæcologists.

(2) *Displacement of presenting part due to low implantation.*—It is rather surprising that this means of diagnosis was not described until 1941 (Ball and Golden). McCort, Davidson and Walton (1944) considered that the method was only applicable with a head presentation, a fœtus of normal size, and just before the onset of labour. They found the average distance from head to pubes (with the patient lying on her side) averaged 3·0 cm. in normal cases, and 4·0 cm. in placenta prævia. Similarly, the head-promontory measurements were respectively 1·7 cm. and 3·4 cm.

Method Employed at the Radcliffe Infirmary, Oxford, 1947–51

During the last three and a half years, the radiological diagnosis of placenta prævia has been based on the demonstration of the placental shadow, together with displacement of the presenting part from the corresponding portion of the pelvic brim.

An analysis of 518 cases examined during the period January 1, 1949, to June 30, 1950, is given at the end of this paper, p. 709.

Placental shadow.—An aluminium wedge-shaped filter is used, which slots into the tube head, where it reduces the intensity of radiation directed towards the less dense tissues of

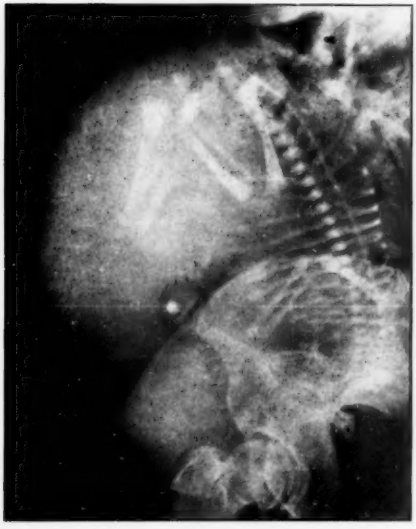

Fig. 1.—Normal anterior placental shadow. (Patient lying on her side.)

Fig. 2.—Normal posterior placental shadow. (Patient lying on her side.)

the anterior part of the abdomen. Without this device, it is difficult to demonstrate both anterior and posterior uterine walls on the same film, owing to the different exposures required.

As implantation is nearly always anterior or posterior, a lateral radiograph is necessary to show the placenta in profile. This used to be taken with the patient lying on her side, but during the last two years, the erect position has been used. In the latter procedure, the fœtus tends to rest directly on the anterior uterine wall, and thereby lessens the possibility of the liquor giving rise to a pseudo-placental shadow.

Displacement of presenting part by placenta prævia.—It seems to be agreed by most authorities, that the lower segment extends some 7–11 cm. upward from the internal os, before the onset of labour. The junction of the upper and lower segments should not therefore be above, nor very much below, the pelvic inlet. It follows that a placenta which is shown to be entirely within the abdomen before labour, is not prævia. On the other hand, evidence of placenta extending downwards into the pelvis, usually, but not always, indicates implantation on the lower segment. Radiological diagnosis depends on the demonstration of placenta at the level of the brim, the accuracy achieved varying with the presenting part.

Head presentations.—In normal cases, the minimum distance between the presenting part and the bony margin of the pelvic inlet, should be slightly greater than the thickness of the intervening uterine muscle. In several hundred lateral radiographs, taken in the erect

position, I have found the head from 0·5 to 1·5 cm. distant from both pubes and promontory, unless its dimensions were small in relation to the pelvic brim. In the latter (Fig 5B) the effect of gravity being greater towards the pubes—the head was often several centimetres from the promontory, but a further lateral view in a semi-erect position, showed it had gravitated backwards, and the gap was now within the range of normal.

In the erect or semi-erect antero-posterior view, the head normally lies in the central pelvic axis, approximately equidistant from the lateral margins of the brim.

If placenta passes through the inlet on to the lower segment, it must increase the minimum distance between the presenting part and the brim. Knowledge of this distance, representing the combined thickness of placenta and uterine muscle, would be some indication of the degree of extension on to the lower segment. The greater the gap, the more likely is implantation on the lower segment to be considerable. Radiologically the distance can be estimated, using the presenting part as though it were a contrast medium. In head presentations the X-ray findings are as follows:

Anterior placenta prævia (Fig. 3).—(1) Anterior placental shadow. (2) Head—pubes displacement.

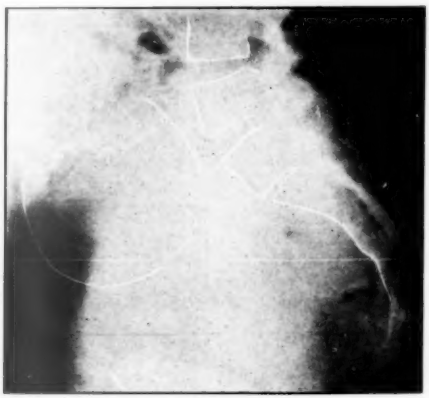

FIG. 3.—Anterior placenta prævia. Lateral pelvis (erect). Head displaced 4·2 cm. above the pubes.

FIG. 4A.—S.C. Posterior placenta prævia. Lateral view (erect). Head 4·2 cm. forward from lumbosacral spine and 1·0 cm. above pubes.

FIG. 4B.—S.C. Posterior placenta prævia. Lateral view (semi-erect position). Forward displacement of head maintained; distance = 3·8 cm.

The head is usually displaced 2½ cm. or more from the pubes. A gap of 4 cm. or more during the last four or five weeks of pregnancy indicates a major degree of placenta prævia but 2½ cm. may be equally significant if the head is also displaced laterally.

Between 28 and 34 weeks a head–pubes distance of barely 2½ cm. without lateral displacement should always be reconsidered after an interval of two to four weeks. Almost invariably the X-ray findings will then be normal, indicating implantation on the upper segment, although probably extending well down.

Posterior placenta prævia (Fig. 4).—(1) Posterior placental shadow. (2) Head—promontory displacement (Fig. 4, A, B).

If the distance between the head and the promontory in the erect position exceeds 2½ cm. it is advisable to re X-ray with the patient reclining backwards. Should the gap be maintained in the second position it should be considered as a true displacement (Fig. 5A). Its

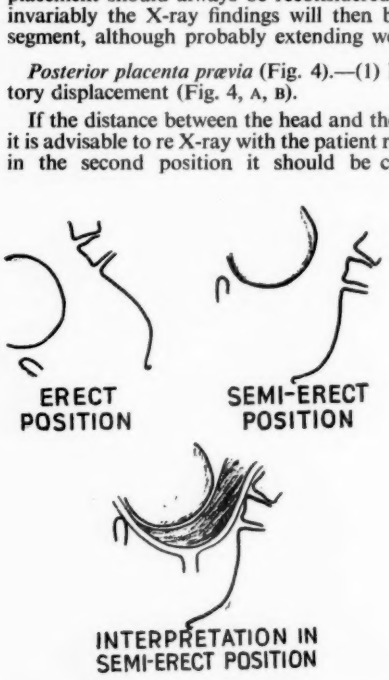

FIG. 5A.—Head-promontory gap in erect position due to posterior placenta prævia.

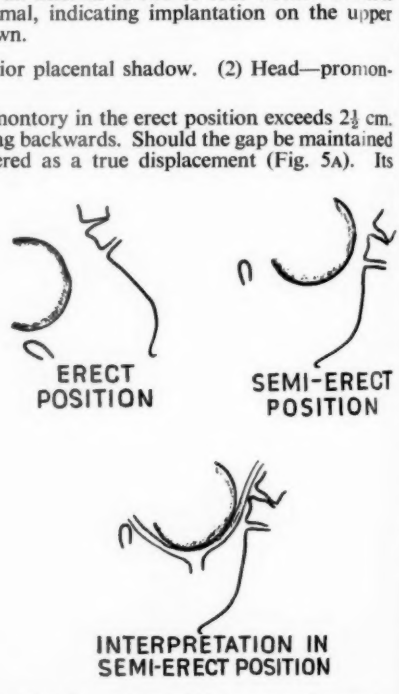

FIG. 5B.—Differential diagnosis of posterior placenta prævia. Head-promontory gap in erect position not due to placenta prævia.

significance will vary (as described under *Anterior placenta prævia*) with the amount of displacement, whether associated with lateral displacement or not, and the stage of pregnancy at the time of X-ray.

Lateral placenta prævia.—Although implantation on the lower segment is usually anterior or posterior it frequently extends on to the lateral uterine wall. In such cases the radiographs show the presenting part displaced not only forwards or backwards but also to one side of the central pelvic axis.

I have only twice found radiographic appearances which suggested a placenta prævia confined to one lateral wall. In each case the presenting part was displaced to one side of the midline but was normally distant from both pubes and promontory.

Differential Diagnosis

(1) *Full bladder.*—The patient should always pass urine immediately before examination. A partly filled bladder may cause a gap of several centimetres between the head and the pubes; if associated with an anterior placental shadow, this may lead to an erroneous diagnosis of placenta prævia.

(2) *Loaded rectum and pelvic colon.*—A large accumulation of fæces in the pelvis may prevent engagement and cause the head to be widely separated from the promontory and, in some cases, from the pubes too.

Fæcal matter produces typical X-ray appearances so that recognition is easy if the placental shadow is anterior and there is no head—pubes displacement to indicate extension into the

pelvis. Confusion may arise with a posterior shadow, but placenta prævia can be excluded, if further X-rays after evacuation of the bowel show a normal head-promontory distance.

(3) *Lax abdominal muscles* (Fig. 5B).—When the mother's abdominal wall is flabby, the presenting part is usually resting directly above the pubes in the erect position, although in extreme cases it may be even further forward in a pouch formed by the sagging abdominal muscles.

If the placental shadow is posterior and therefore continuous with the extremely wide head-promontory gap, the appearances in the erect radiograph are identical with posterior placenta prævia. Although the state of the abdominal musculature is obvious on examination of either the patient or the radiograph, a further examination should be carried out in the semi-erect position; if the head is then normally distant from the promontory, the possibility of co-existing placenta prævia can be excluded.

(4) *Pelvic tumours.*—Displacement of the presenting part is occasionally due to either fibroids or an ovarian cyst. Differentiation from placenta prævia may be impossible radiographically, if the soft tissue space separating the head from the pelvis is continuous with the placental shadow. Suspicion should be aroused when there is no such continuity, a good example of which is illustrated in Fig. 6A, B, C; in this case, which had not been diagnosed clinically prior to radiography, the outline of the tumour could be seen through the gas-filled lumen of the bowel.

In my radiological experience, the incidence of pelvic tumours causing displacement of the presenting part has been small, compared with that of placenta prævia. Usually the presence of a tumour was known to the obstetrician, or it was suspected where the patient was an elderly primigravida, especially if fibroids had been palpated on the abdominal part of the uterus.

Breech presentations.—There are two main reasons why the radiological diagnosis of placenta prævia is less reliable with breech presentations. Firstly the breech is irregular in

FIG. 6A.

FIG. 6C.

FIG. 6B.

FIG. 6A.—J.C. Fibroid in posterior pelvis; contour visible in radiograph (dotted line). Head-promontory displacement. Head-pubes distance normal.

FIG. 6B.—J.C. Posterior pelvic fibroid. Normal anterior placental shadow (erect). Dotted line shows anterior contour of uterus.

FIG. 6C.—J.C. Posterior pelvic fibroid. Antero-posterior view (semi-erect). No lateral displacement of head.

shape and therefore fits less closely than the ovoid skull into the lower pole of the uterine cavity; secondly, owing to technical difficulties, its translucent outline representing subcutaneous fat is not consistently visible in the routine lateral radiograph. Nevertheless in spite of these disadvantages, the method need not be discarded on discovering a breech presentation.

A major degree of placenta prævia can be excluded when the breech is dipping symmetrically into the inlet, and there is no wide separation from either pubes or promontory. As similar findings may occur when the thin lower edge of a placenta crosses the brim latero-anteriorly or latero-posteriorly, only a major degree of placenta prævia should be excluded without re-examination.

The diagnosis of placenta prævia follows the same principles as in head presentations, but tends to be less accurate. Owing to faulty accommodation, the amount of displacement is very often disproportionately greater than would be expected for the degree of placenta prævia which is subsequently found. For this reason when the breech is widely separated from either pubes or promontory, I make a practice of suggesting a further X-ray examination following version; the obstetricians have usually co-operated, and the baby has been turned in the X-ray department. Further films, taken immediately afterwards, have shown, either the head fitting snugly in the brim, and thus excluding placenta prævia; or displacement was still present but usually less than with the breech.

Malpresentation.—Regardless of the presentation, I have found that a diagnosis can eventually be made, if not at the first examination, in nearly every case. Interpretation is not difficult when the fœtus lies transversely, the disadvantages differing only in degree from those encountered in breech presentations.

With a transverse lie, placenta prævia can be excluded if the lateral radiograph shows the fœtus as a whole immediately above the pelvic inlet and some 2½ cm. or less from both pubes and promontory. More often, perhaps, the nearest fœtal parts are several centimetres away from one or both of these bony landmarks, in which case it is advisable to postpone diagnosis, and suggest re-examination after version.

Occasionally a patient, examined for the first time in the last two or three weeks of pregnancy, is found to have a transverse lie, the fœtus being some 7 or 8 cm. from pubes or promontory. If the site of displacement is continuous with a placental shadow extending only about half-way up the uterine wall a major degree of placenta prævia can be diagnosed without any further examination.

A New Approach to Amniography

The following is a brief account of this work which was carried out with the collaboration of Mr. Gordon Lennon.

It is only on rare occasions that the slight risk inherent in any kind of amniography seems to be justified. In such cases we have employed two variations of the usual procedure, in order to reduce the danger to a minimum.

(1) Lipiodol was first used, the amount injected varying from 3 to 5 c.c. By suitable posturing of the patient it was possible, as I had expected, to demonstrate a layer of contrast medium on either the anterior or posterior wall of the lower segment. A striking and unexpected sequel revealed in films taken the following day was an almost complete radiopaque outline of the baby, which persisted until delivery. Presumably the continual movements of the fœtus had rubbed the lipiodol into the vernix, forming an emulsion on the baby's skin.

(2) Although Pyelosil belongs to the same group as Uroselectan, Skiodan, &c., of the original method, I used it in a different way. 20 c.c. of a 70% solution was injected into the uterus with the patient in a half-sitting position, following which she sat upright to allow the heavier contrast medium to sink through the liquor to the bottom of the uterine cavity. In this way the maximum radiopacity of the liquor was obtained where it was most wanted—in the lower segment.

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X-RAY LOCALIZATION OF PLACENTAL SITE IN 518 CASES (RADCLIFFE INFIRMARY, OXFORD)
(January 1, 1949 – June 30, 1950)

I. *Appearances of Normal Implantation—*

Anterior	215
Posterior	224
"Fundal"	16
Total	455

Some Clinical Features in 455 *Radiologically Normal Cases*

A. *APH* — Total 52

Cervical polyp or erosion demonstrated	19
Placenta prævia ditto	Nil

B. *No APH* — Total 403

Placenta prævia demonstrated	1

C. *Clinical verification of placental site—*

At C.S.	21
During manual removal	5
Total	26
X-ray localization correct	26

II. *X-ray Appearances of Placenta Prævia—*

A. *Complete clinical confirmation—*

At C.S.	26
Vaginal delivery	6
	32
Anterior (or predominantly ant.)	11
Posterior (or predominantly post.)	21

B. *Other clinical evidence of low implantation—*

Trauma to placenta by D-S catheter	2

C. *Not confirmed clinically* — 10

Total 44

III. *Appearances of Normal Implantation Following Earlier X-ray Evidence of Low Placenta—*

Anterior wall	15
Posterior wall	4
Total	19

COMPARISON WITH PREVIOUS SERIES

October 1, 1947–December 31, 1948 (15 months)	No. of cases	January 1, 1949–June 30, 1950 (18 months)	No. of cases
X-ray appearances of low implantation	73	Final X-ray appearances of low implantation	44
Complete clinical confirmation obtained	22	Complete clinical confirmation obtained	32
Proportion of proved/unproved	30%	Proportion of proved to unproved cases	73%

Mr. Samuel Davidson (*Birmingham Maternity Hospital*):

INTRODUCTION

Dr. Frank Reid's paper has indicated an additional valuable method and aid in the localization of the placenta.

It falls to my lot to evaluate this diagnostic procedure obstetrically, to estimate its need and, above all, to place it in its proper perspective in relation to clinical experience and judgment in the diagnosis and management of cases of possible placenta prævia and of cases of ante-partum hæmorrhage, where the causative factor is temporarily in doubt.

CLINICAL ASPECT

At the discussion on placenta prævia (*Proc. R. Soc. Med.*, **44**, 121) it was asserted by Macafee, Marshall and Snaith that, in their experience, the diagnosis of placenta prævia was possible in the vast majority of cases, on consideration of the history and on abdominal palpation alone. In consequence, they advocated the avoidance of vaginal examination prior to treatment by Cæsarean section, in cases where the diagnosis of placenta prævia had been made, and it is probably true to say that there is a large body of opinion in agreement with this view.

None the less, such a radical and dogmatic claim in diagnosis can only be accepted if it can be applied to obstetricians in general as well as to experienced clinicians. I have, therefore, reviewed all the cases of ante-partum hæmorrhage and of proved placenta prævia occurring during 1950 in the Birmingham Maternity Hospital, on the staff of which there are 7 consultants. The analysis of these cases has been carried out purely with a view to establishing the correctness, or otherwise, of clinical interpretation in diagnosis.

TABLE I.—BIRMINGHAM MATERNITY HOSPITAL 1950

Cases of A.P.H. (all causes)
and placenta prævia (all cases)

Total: 87

Placenta prævia	Accidental hæmorrhage	Other cause
41	45	1

Non-toxæmic	Toxæmic
34	11

The combined total of cases of ante-partum hæmorrhage from all causes and of placenta prævia without hæmorrhage admitted during the year was 87.

The case due to another cause was an unusual case of hæmorrhage simulating a placenta prævia. Examination under anæsthesia showed no evidence of a low-lying placenta and thereafter the membranes were ruptured on the assumption that the hæmorrhage was accidental. This, however, failed to control the hæmorrhage which was fairly free. The cervix was then inspected and it was found that the hæmorrhage, which was arterial in origin, was arising from a vessel on the vaginal surface of the anterior lip. This was satisfactorily controlled by the temporary application of a sponge forceps and labour, which was already established, was allowed to proceed. Unfortunately, this patient later developed a concealed accidental hæmorrhage which resulted in the death of the fœtus.

TABLE II.—ACCIDENTAL HÆMORRHAGE

(Total: 45)

Cases diagnosed on admission
24

Diagnosis: correct	Incorrect
23	1

Cause: Non-toxæmic	Toxæmic
12	11

The total number of cases finally diagnosed as cases of accidental hæmorrhage was 45.

The case of incorrect diagnosis was an elderly primigravida who had been in hospital for a fortnight with a severe degree of toxæmia when slight ante-partum hæmorrhage occurred at the 37th week. The head, which was small, was engaged in the pelvic brim. A Cæsarean section was carried out because of the toxæmia and ante-partum hæmorrhage and at operation a major degree of placenta prævia was discovered.

It is obvious, therefore, as is to be expected, that there is no great difficulty in the accurate diagnosis of cases of accidental hæmorrhage of toxæmic origin. When a co-existent placenta prævia is present in a toxæmic case it may be overlooked.

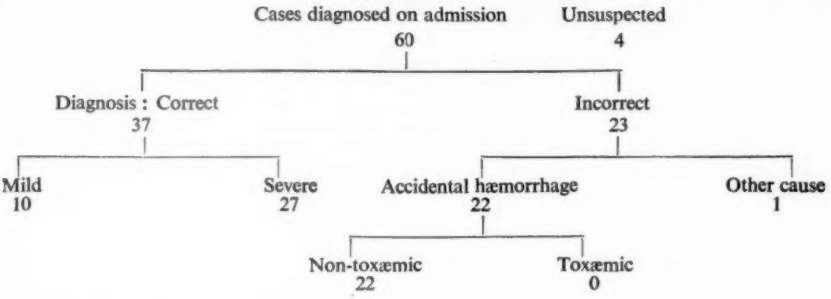
In the 12 correctly diagnosed non-toxæmic cases it was found that the diagnosis was aided, clinically, by finding engagement of the presenting part in half of the cases, and by the history of the hæmorrhage and the irritability of the uterus in the other half. Moreover, some of these cases had, in addition, some degree of concealed hæmorrhage producing localized pain and tenderness, thus indicating the site of the placental detachment.

The total number of cases finally diagnosed as cases of placenta prævia was 41. At some stage, however, this diagnosis was made in 60 cases. This high figure is due, of course, to the fact that in many of these cases the diagnosis was doubtful, but as immediate active treatment was not thought to be advisable it was felt that, in the first place, they should be placed in the worst possible category.

TABLE III

PLACENTA PRÆVIA

(Total: 41)



The diagnosis was found to be correct in 37 of these cases and incorrect in 23. There were 4 cases in whom the condition was quite unsuspected. Of those correctly diagnosed as placenta prævia 10 were classified as mild and 27 as severe.

Of the 23 cases incorrectly diagnosed there proved, in the end, to be 22 cases of accidental hæmorrhage and 1 case due to another cause, which has already been detailed. All of these 22 cases of accidental hæmorrhage were of non-toxæmic origin. A further review of these 22 cases, provisionally diagnosed as placenta prævia in the first instance, shows that some of them were later assessed clinically to be, in point of fact, cases of accidental hæmorrhage, on account of the subsequent descent of the presenting part. When these 22 cases were seen initially, however, there were 14 in which the head was high with added deflexion in 3 of these cases. There was one case of transverse lie, one of oblique lie with the breech in the iliac fossa, and 3 cases of breech presentation with non-engagement.

It is clear, therefore, that there is here a group of cases of no inconsiderable proportion diagnosed initially as placenta prævia, temporarily treated as such and later found to be cases of non-toxæmic accidental hæmorrhage. This analysis therefore refutes the contention of the clinical observers who maintain that they can almost always be certain when the patient has a placenta prævia on history and abdominal palpation alone. It further indicates a group of cases in which X-ray localization of the placenta will be desirable once its accuracy is established.

TREATMENT

In none of these cases was radiography employed in assisting the diagnosis. It will be interesting, therefore, to observe how these cases were managed and treated.

Of the 10 mild cases of placenta prævia 3 required no treatment, 6 were treated by rupture of the membranes and 1 was treated by repeat Cæsarean section. Of the 27 severe cases of placenta prævia 22 were delivered by Cæsarean section and 5 vaginally. All the 22 cases of non-toxæmic accidental hæmorrhage were delivered by the vaginal route. The 4 unsuspected cases, details of which will now be given, were all cases of severe degree and were treated by Cæsarean section:

Case 1.—Hydramnios with an unstable lie. A surgical induction had been performed, the head had remained high and examination under anæsthesia revealed an anterior wall placenta prævia of second degree.

Case 2.—Unstable lie with a normal pelvis. In view of the unstable lie and other circumstances Cæsarean section was performed and a severe degree of placenta prævia discovered at operation.

Case 3.—Primigravida with an oblique lie with the breech in one iliac fossa. X-ray examination elsewhere had suggested placenta prævia. Examination under anæsthesia did not confirm the presence of placenta prævia but at Cæsarean section a second degree placenta prævia was found. This case is of special significance and will be referred to in more detail later.

Case 4.—Primigravida with the head above the brim in the later weeks of pregnancy, there being no apparent reason for this abnormality. The pelvis was normal. Pregnancy continued until the 42nd week, a medical induction was performed and when labour commenced there was severe ante-partum hæmorrhage, Cæsarean section was performed and a third degree placenta prævia discovered.

Two further cases are of interest in that placenta prævia was suspected but not confirmed until after slight ante-partum hæmorrhage had occurred. The diagnosis, even then, was not finally accepted and examination under anæsthesia was carried out in both these cases.

Case A.—This patient was gravid: 2. The head was found to be high and lying towards the left iliac fossa at 35 weeks—it could not be pushed into the brim. During early labour at 41½ weeks hæmorrhage occurred. Examination under anæsthesia was carried out confirming the presence of a severe degree of placenta prævia and Cæsarean section performed.

Case B.—This patient was gravid: 2. The breech was presenting and was high. A slight show had occurred at 36 weeks and at 38 weeks examination under anæsthesia was performed to confirm the presence of placenta prævia. This led to torrential hæmorrhage and a very rapid Cæsarean section was performed.

In 5 of these 6 cases X-ray investigation, if accurate, would have helped materially in providing an earlier diagnosis of the exact state of affairs, and would have led to the avoidance of the risks associated with a doubtful diagnosis and, even more so, the avoidance of the dangerous practice of performing digital vaginal examination in cases of severe degree of placenta prævia. In this type of case I find myself in entire agreement with Macafee, Marshall and Snaith, that where placenta prævia of major degree is probable, digital vaginal examination is to be condemned.

The remaining case (Case 3 from the unsuspected group) requires further elaboration because in this case radiological diagnosis was available but was ignored. This was a primigravida, aged 30, with an oblique lie—the breech lying in the right iliac fossa. She was referred by her doctor at 38 weeks to the Ante-Natal Clinic, and the following X-ray report was enclosed from films taken at 36½ weeks:

"Single fœtus, breech presentation. The breech lies well in front of the pubes in the erect posture, the dorsum is to the right, the placenta is posterior and there may be a marginal placenta prævia, which would account for the high position of the breech."

The obstetrician concerned seems to have been somewhat sceptical of this report and not a little amazed at the audacity of the radiologist. Examination under anæsthesia was performed without preparations for Cæsarean section. The os was closed and it was only found possible to exclude a central placenta prævia. Spontaneous version had taken place the day before and it was now noted that the head could not be made to enter the brim. At no time had there been any hæmorrhage. The patient was sent home and readmitted a week later on account of a transverse lie. Cæsarean section was decided upon on account of the unstable lie and disproportion without mention of placenta prævia. At the operation the placenta was found on the posterior wall and extended to within one inch of the internal os. There was a battledore insertion of the cord into the upper margin of the placenta.

Examination Under Anæsthesia

Of the proved mild cases of placenta prævia 3 were examined vaginally under anæsthesia and in 7 cases this was not found necessary. Of the severe cases of proved placenta prævia vaginal examination under anæsthesia was carried out in 17 of the 27 cases and not performed in 10 cases. Of these 17 cases in which vaginal examination was carried out, severe hæmorrhage occurred during the examination in 8 cases. In the non-toxæmic group of accidental hæmorrhage (Table III) vaginal examination under anæsthesia was carried out in 8 of the 22 cases and in 14 it was not found necessary.

In this hospital, therefore, there is still a tendency to examine cases vaginally where placenta prævia, even of major degree, is suspected, and this was carried out in two-thirds of the cases, resulting in excessive additional hæmorrhage in half of the cases so examined. There is a good case for the avoidance of such an examination even though in some cases the examination will prevent an unnecessary Cæsarean section. If accurate radiological assessment were available in cases of suspected placenta prævia, it would result in the better management of such cases and would eliminate the need for vaginal examinations with their attendant risks. Similarly, accurate X-ray localization of the placenta might rule out placenta prævia as the cause of the bleeding or malpresentation.

Hospitalization

Placenta prævia mild.—Of the 10 cases 8 were in hospital only one to two days before delivery. There were only 2 cases of more prolonged stay, one of fifteen days and another six weeks.

Non-toxæmic accidental hæmorrhage.—Of the 22 cases of non-toxæmic accidental hæmorrhage presumed to be cases of placenta prævia in the beginning, 13 were delivered within two days of admission, 3 were in hospital for three days before delivery, a further 4 were in-patients for less than a week, and 2 were in hospital for ten days before delivery. Of the 12 cases of non-toxæmic accidental hæmorrhage diagnosed as such, 7 were in hospital for two days or less before delivery, 2 were in hospital for a week and 3 for a fortnight before delivery.

Placenta prævia severe.—Of the 31 cases of severe degree of placenta prævia, which includes the 4 unsuspected cases, 16 of these were in hospital for less than three days before delivery, 3 for less than a week, 6 for seven to ten days, 3 for about a fortnight, and 3 required hospitalization for between five and six weeks. Two cases were discharged after the initial hæmorrhage had subsided and required readmission on account of further bleeding.

No satisfactory deductions can be made from these figures on hospitalization.

Discussion

In consideration of the question of the value of radiological investigation in the localization of the placenta it is of primary importance that agreement be first reached as to whether this diagnostic aid has been found to be of sufficient accuracy for general use. It was argued by Professor F. J. Browne at the recent discussion on placenta prævia, that the previous published work by Dr. Reid on this subject had not shown a sufficient degree of accuracy even in his expert hands, and he felt that in the hands of less experienced personnel the method would prove of little value. However, Dr. Reid has shown in his more recent work an increased degree of accuracy in radiological localization of the placenta and it would seem that with enthusiasm for this work, and careful follow-up of cases by radiologists in other centres, the method could prove to be of definite value to clinicians.

It must be clearly understood that, as with other forms of investigation, this method must be used only as an adjunct to careful clinical observation and must never be considered to be the final answer. Furthermore, there can be no place for this diagnostic procedure as a routine measure in obstetric practice.

The assertion by Macafee, Marshall and Snaith that correct diagnosis in cases of placenta prævia can be made entirely on the history and on abdominal palpation is, in the light of the present investigation, untenable. It is probable that obstetricians of their experience can be reasonably certain in a large proportion of cases that they are dealing with a case of severe degree of placenta prævia, but this degree of accuracy cannot be obtained by the majority of those responsible for obstetric care in hospitals. The present investigation has shown that for the average clinician there appears to be a need for help in the establishment of a definite diagnosis where, for the time being, placenta prævia is merely suspect.

It should also be of considerable value in determining, if prævia, the exact position of the placenta, i.e. whether situated mainly anteriorly or posteriorly, thus assisting in the management of these cases. In particular where a posterior position is discovered, as Stallworthy has emphasized, the treatment may need to be adjusted in favour of Cæsarean section in the interests of the child.

With regard to hospitalization and the occupancy of beds in ante-natal wards by cases of ante-partum hæmorrhage, the assertion has been made by Macafee that, in his experience, no admission could have been avoided by the application of soft tissue radiography. This is probably true, but by the application of soft tissue radiography some cases of placenta prævia will be diagnosed before they could be suspected clinically, and might require admission to hospital as a safety measure on that account. But, surely, the main value to be gained from radiography, in this respect, would be in those cases of ante-partum hæmorrhage already admitted to hospital for observation, where the diagnosis lies between a possible placenta prævia of unknown degree and non-toxæmic accidental hæmorrhage. The problem looked at from a different angle from that of Macafee would be one in which the knowledge gained by soft tissue radiography would allow the discharge of the patient, safely, from hospital when it had been shown that a severe degree of placenta prævia was not present and when the hæmorrhage had subsided. Radiological localization is not designed to prevent admission to hospital, but rather to permit of discharge from hospital. It might thus help to limit the stay of cases of ante-partum hæmorrhage found to be due to non-toxæmic causes or mild degrees of placenta prævia, and allow of earlier resumption of the patient's domestic responsibilities.

Stallworthy has mentioned a group of 25 cases in which such discharge from hospital was possible after radiological investigation was carried out, and in no cases was this discharge regretted. Stallworthy specifically mentions that in these cases no vaginal examination was carried out, but it is important to emphasize that at least a speculum examination should be performed before such a patient is allowed to be discharged. One must assume that he was referring to digital vaginal examinations only.

Just recently I had a case which illustrates this point forcibly: A patient, aged 35, gravid: 3, was admitted to hospital at 28 weeks on account of ante-partum hæmorrhage. The hæmorrhage was bright and continued for several days after admission and, later, this patient was demonstrated as a probable case of placenta prævia. Had soft tissue radiography been carried out in this case the placenta would have been found to have been normally situated

and without careful assessment of the case this patient might have been erroneously discharged once the hæmorrhage had subsided. On speculum examination, however, which was not carried out until the patient had been in hospital for a fortnight, a severe degree of carcinoma of the cervix was discovered.

It is quite clear, from the present investigation, that at the Birmingham Maternity Hospital, and probably at many other hospitals, in contradistinction to the methods practised by Macafee, Marshall, Snaith and others, many digital vaginal examinations are being carried out under anæsthesia in cases where the diagnosis is probably that of a severe degree of placenta prævia. As has been shown from the present figures, two-thirds of these cases were subjected to vaginal examination and in one-half of these dangerous hæmorrhage was produced. Macafee, Marshall and Snaith, when omitting the vaginal examination, admit that they may occasionally perform an unnecessary Cæsarean section, but they do not state how many, and it would appear that there is a definite place for radiological investigation as the *via media* in the classification of these cases, at present handled so diversely. This would then clearly reduce the necessity for examination under anæsthesia to those cases considered not to be due to placenta prævia of major degree, as advocated by the three obstetricians mentioned. This examination may still be necessary in order to exclude the presence of a severer degree of placenta prævia than indicated radiologically, which may occur when the placenta happens to be unusually thin.

Though soft tissue radiography will not always determine the line of treatment, it may prove to be of definite value in the following cases:

(1) In all cases of suspected placenta prævia prior to the time when active treatment is indicated, in other words before practical viability, and in the absence of severe hæmorrhage.

(2) In non-toxæmic cases of accidental hæmorrhage with a coincident malpresentation or malposition of the fœtus.

(3) In cases of malpresentation without, or with, any other reasonable explanation for this malpresentation being present.

Before carrying out this investigation I shared the opinion of other clinicians that there was probably no necessity for additional aid in the localization of the placenta, but from this review of a year's cases in the Birmingham Maternity Hospital, that outlook has had to be revised.

SUMMARY

(1) There appears to be a definite need for additional aid in the localization of the placenta such as might be provided by soft tissue radiography.

(2) The method must provide a sufficiently high degree of accuracy in diagnosis when assessed by radiologists generally.

(3) It must be employed in selected cases only and not as a routine method of investigation. The types of cases have been enumerated.

(4) Soft tissue radiography should not be considered as more than an aid to diagnosis and management. It must never be allowed to replace careful and complete clinical assessment.

(5) It should, however, help to eliminate the employment of unnecessary and dangerous digital vaginal examinations.

(6) In cases of ante-partum hæmorrhage of early onset it may allow earlier and safer discharge from hospital.

Professor J. Chassar Moir (*Oxford*): When in 1934 Snow and Powell claimed that the placental site could be revealed by what has come to be called soft tissue placentography, they aroused interest but at first no great enthusiasm. Doubtless this was because the claims were too high and were, as we now know, vitiated by some serious inaccuracies. In 1940, Dippel and Brown set the new method squarely before obstetricians, and they and later workers—not least Dr. Reid by his present work—have put the method on a sound foundation.

Ten years ago I started to test the method in the Nuffield Department of Obstetrics and Gynæcology at Oxford. Soon I began to realize that the definition of the placental site as stated by the early workers was much too vague. Dippel and Brown had been content to describe it thus: "*The placenta is localized in the region where the structure between the outer uterine wall and the fœtal soft parts are definitely increased in thickness.*" I soon found that amniotic fluid even when present in normal quantity would in some circumstances fulfil this definition and so constitute a major pitfall in diagnosis.

A series of experiments, some of which I shall now mention, showed that the uterine wall, the placenta and the amniotic fluid all threw shadows of indistinguishable density.

(1) The placenta, after delivery, was suspended, cuplike, in order to show, on lateral X-ray projection, its inner wall. A second X-ray was then taken after pouring amniotic fluid into the placenta. In the resulting radiograph the presence of the fluid caused a complete disappearance of any trace of the inner placental surface.

(2) When radiographing the pregnant abdomen in a case showing a thickened anterior uterine wall, the effect of external pressure was noted. There was a great reduction in the thickness of the shadow which indicated, it seemed, that in the case under observation, part at least of the shadow was composed of amniotic fluid.

(3) Most convincing of all was the injection of air into the amniotic sac, and the obtaining of a radiograph with the patient so positioned that the air was caused to float into the area of thickened uterine wall. This experiment, repeated in several cases, clearly showed that certain uterine thicknesses coming within Dippel and Brown's definition of placental site were, without any doubt, amniotic fluid shadows and nothing else.

At that time I was chiefly concerned in drawing attention to the need for a stricter definition of what could safely be accepted as, and what could not be safely accepted as, a placental shadow; and a paper on this subject was in due course published in the *American Journal of Obstetrics and Gynæcology*.

More recently, Dr. Reid has taken up the subject afresh in Oxford, and has acquired high skill in diagnosing placental shadows and in differentiating them from other forms of uterine wall thickening. In particular, he has made use of the effect of gravity on the fœtus in order to disperse any amniotic fluid from a supposed placental area. His second method, applicable to cases of placenta prævia, is quite distinct from the first although allied to it. By it he demonstrates a constant displacement of the fœtal head from sacral promontory, or pubes, or both, in accordance with the position of the placenta—which displacement remains unaltered even when the woman is X-rayed in changed position.

What does elaborate radiography do that a simple clinical examination of the abdomen will not do? It can be contended that, so far as the diagnosis of placenta prævia is concerned, the evidence we have heard is nothing more than a roundabout way of showing what every good clinician already knows—namely, that placenta prævia has as a cardinal sign the non-engagement of the fœtal head in the pelvic brim and a refusal of that head to sink into the brim when it is manipulated over the region.

Now, if every case of placenta prævia was typical, and if the placenta always reached well down into the pelvis, and if the patient was always thin and easily palpated, and if every obstetrician had great clinical experience and fine judgment—then the pursuit of the placenta with an X-ray tube would be merely an entertaining, and possibly harmless, academic pastime. But as everyone knows, these conditions do not always obtain; and, speaking for myself, I have often been glad to have the radiologist's help. And the evidence may be valuable when it is in the negative, as well as when it is in the positive sense. Important indeed it is to know that the placenta is in the prævia position; but, faced with the management of a case of undiagnosed ante-partum hæmorrhage, it may also be very helpful to learn that a major degree of placenta prævia can be safely excluded.

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Mr. J. C. McClure Browne (*London*): *Localization of the placenta by means of radioactive sodium.*—

REVIEW OF EXISTING METHODS

The earliest method of locating the placenta was by means of the souffle. No figures can be discovered for the accuracy of this method. Various methods have been described in recent years, using X-rays with contrast media; such methods are amniography, intravenous placentography, and cystography. More recently soft tissue radiography (first used for this purpose by Snow and Powell, 1934) has been used with some success. All these methods are tedious and require expert radiography and interpretation, though Reid reports successful results in 41 out of 42 cases. A comprehensive review of the literature on the subject is given by Reid (1949). The work done up to the present seems to be concerned chiefly with the exclusion of placenta prævia.

Previous observations on the circulatory physiology of the placenta by Barcroft and others are open to the objection that in reality *uterine* blood flow was studied, and the order of magnitude of flow in the placenta was deduced therefrom. These methods, moreover, were not readily applicable to the human subject.

In an attempt to obtain direct information in the human it seemed, therefore, necessary to be able to locate the placenta in the uterus before birth of the child, and without the necessity for general anæsthesia and laparotomy, so that blood samples could be obtained from its site for analysis.

At first thought we turned to soft tissue radiography, but there were various technical difficulties which prevented our using this method. Knowing that radio-active iodine could be used to outline the thyroid, it was decided to use a non-persistent tracer element, and Na^{24} seemed most suitable for our purpose. This isotope, which has a half-life of sixteen hours or so, is readily diffusible and rapidly excreted.

For advice as to dosage I am indebted to Dr. Constance Wood, Director of the M.R.C. Radiotherapeutic Research Unit at Hammersmith Hospital.

Method

Approximately 50 microcuries of radio-active sodium Na^{24}, in the form of 5–20 ml. of sterile isotonic saline, are injected into a suitable antecubital vein. After allowing about thirty seconds for the Na^{24} to mix in the blood stream, radioactivity measurements are made over the abdominal region. For this purpose a counter tube, without lead shield but with the window screened to prevent entry of particles, is used in conjunction with a counting rate meter.

A mains operated instrument has also been found to be satisfactory, though not so convenient.

The counting rate over the area of the uterus and other regions is measured with the end of the counter tube in contact with, and with the axis normal to, the skin. From time to time the counter is placed over the heart, and the observed reading taken as a reference level. The counting rate over the fundus of the uterus is about $\frac{1}{2}$ to $\frac{2}{3}$ of that observed over the heart, and is slightly higher on the right side owing to the radiation from the liver. The observed counting rate decreases rapidly towards the lower uterine pole, and over the lower segment of the uterus it is only one-fifth of that over the heart.

The method depends on the fact that the placenta is essentially a pool of blood and therefore represents a local accumulation of Na^{24} so long as the bulk of the isotope remains in the circulation. However, since the administered Na^{24} rapidly diffuses out of the vascular system (Burch, Reaser and Cronvich, 1947) useful observations can only be obtained within a few minutes of injection.

When the placenta is situated on the anterior wall of the uterus its site is indicated by a region where the counting rate is considerably higher than that over the uterus generally, and is almost equal to that observed over the heart. If such a region is not found, it is concluded that the placenta is located on the posterior wall. In cases of posterior location where the placenta is not centrally situated, it is usually possible to find out on which side it lies by differences in the counting rate; but the counting rates observed will be considerably lower than that found over the heart.

The actual position of the placenta was subsequently determined by Cæsarean section, manual removal, or free aspiration of blood from the supposed placental site. In some cases, where free aspiration had been obtained, the placental site was confirmed by one of the other methods. Indeed, so striking was correlation between the findings by the aspiration method and those on Cæsarean section and manual removal that we came to regard free aspiration of blood as definite evidence of the presence of the placenta at that point.

In the case of complete posterior position of the placenta, where there was no part to be detected on the anterior wall of the uterus, no attempt at aspiration could be made, and the case was discarded as not suitable for our purposes.

Radiation Dosage

Radioactive sodium administered intravenously is known to be rapidly distributed in a uniform manner in the extracellular fluid throughout the body (Burch *et al.*, 1947). Assuming uniform distribution, and neglecting loss by excretion, the total radiation dose received by the tissues of both mother and fœtus when 1 μC of Na^{24} per kilo body-weight is used, can be shown to be approximately 0·1 equivalent roentgens (Marinelli, Quimby and Hine, 1948). This is the currently accepted maximum permissible *daily* dose (Medical Research Council,

1949), and also compares very favourably with the estimated radiation dose received by the patient when the placenta is located by radiological methods.

Martin (1947) estimates a skin dose of the order of 10 roentgens per exposure while the ovaries, and presumably the fœtus, received 0·1 to 0·5 roentgen as a result of a single radiograph.

The results in 118 cases are presented.

Total cases	118
Confirmed by C.S., manual removal or puncture	56
Correct	50
Incorrect	6
Confirmed by C.S. or manual removal	26
Correct	23
Incorrect	3
Confirmed by puncture alone	21
Correct	18
Incorrect	3
Predicted as posterior	62
Posterior confirmed by C.S. or manual removal	9
Correct	7
Incorrect	2

Cases of Special Interest

In 3 cases of intra-uterine death no localization could be obtained long before Spalding's sign became positive. This suggests that the placental circulation had shut down. It might therefore be useful as a test of intra-uterine death.

In 2 cases of antepartum hæmorrhage the placenta was predicted as fundal. Accidental hæmorrhage was predicted and was subsequently confirmed by Cæsarean section.

In 3 cases of antepartum hæmorrhage, placenta prævia was predicted and confirmed at examination under anæsthesia and Cæsarean section, but these were all anterior placentas.

Discussion.—The method described was developed primarily for research purposes, but it was natural to hope that it might find an application in the diagnosis of placenta prævia. Even with the limitation of equipment at present available it has sometimes been possible to show, by virtue of high readings obtained over the lower uterine segment, that the placenta has a low insertion, but failure to obtain these high readings does not, in our opinion, exclude placenta prævia. It must be remembered that the nearer the symphysis, the greater the amount of fat intervening between the counter and the uterus, and the ovoid shape of the uterus results in the lower pole being still further away from the counter.

Over the lower part of the abdomen the counting rate is usually considerably lower than that at the fundus. Where this decrease is not obtained, it is reasonable to suppose that the placenta is present. In other cases of placenta prævia, however, the low-lying portion is thin and membranous, and could not be expected to contain as much blood as the upper, thicker portion, so that a positive result is not obtained.

Nevertheless, in spite of the relative crudity of this technique the results have been sufficiently correct to encourage the hope that it may be possible to use radio-active isotopes in the clinical diagnosis of placenta prævia.

For the purpose of obtaining maternal blood from the placenta in situ, however, the method is simple and adequate, and 5 to 10 ml. of maternal placental blood can be obtained by aspiration.

In closing, I would offer a word of warning to anyone who might be tempted to use the method of aspirating blood from the placenta.

The needle should not be advanced too rapidly, and aspiration must be attempted with each advancement. On one occasion, early in this series, the child was born markedly anæmic, and old blood was present in the amniotic fluid. On careful examination of the amniotic surface of the placenta it seemed that the point of the needle had torn a fœtal vein on the amniotic surface of the placenta. This is the only untoward result we have had. The child was transfused and made a good recovery.

SUMMARY

The various methods of locating the placenta in the intact human uterus are briefly reviewed, and a simple new method is described in which radio-active sodium is used. This method is at present chiefly applicable to the problem of obtaining maternal placental blood for analysis and is of little value in the diagnosis of placenta prævia but the possibility of development of an isotope method of diagnosis of placenta prævia is envisaged.

It is also found that the failure to obtain any localization of the placenta is strongly suggestive of fœtal death *in utero*.

I am indebted to Professor James Young and later to Mr. Charles Read for the clinical facilities for this work, and I would record with pleasure the constant assistance of Mr. Veall of the M.R.C. Radio-elements Research Laboratory.

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Section of Pædiatrics

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[*January* 26, 1951]

DISCUSSION ON CYCLICAL VOMITING AND ALLIED PERIODIC DISORDERS OF CHILDHOOD

Dr. C. K. J. Hamilton (*Taunton and West Somerset Hospital*): The classical type of cyclical vomiting is by no means very common, and would appear to be rather less frequently met with to-day than in the past. This may possibly be due to the general realization that the thin nervous type of child is often made worse by attempts to build him up with fatty foods.

The family history is often instructive. These children tend to come of a nervous stock; other members of the family may be fellow sufferers, or be subject to travel sickness and the like. One or other of the parents is not infrequently a victim of migraine.

The attacks start at about 3 years old and tend to cease at about 10 or 12. Boys and girls are equally affected; the late Sir Frederick Still (1918) found that, in a series of 50 cases, 24 were boys and 26 girls. An attack may be precipitated by mental or physical strain and also by some dietary indiscretion. The onset of the illness is, as a rule, sudden, but there may be a prodromal period of listlessness with excessive yawning and drowsiness. The first sign is vomiting, there appears to be some delay in the emptying of the stomach and food taken some considerable time before is vomited. This is similar to the state of affairs found in migraine, and may be due to over-sympathetic stimulation. Later the vomit consists of bile-stained mucus and finally even sips of water are returned at once. The illness develops rapidly and indeed often presents a very alarming picture. The lips become dry, the tongue furred, and the breath smells heavily of acetone. Intermittent abdominal pain, referred to the neighbourhood of the umbilicus, is a common symptom. Extreme nausea is a very constant feature, and is often accompanied by headache and giddiness. Great pallor of the lips and face is typical. The child may be drowsy or almost comatose, while at other times he is excessively restless. The temperature may be raised, but not invariably so. Convulsions and lapses of consciousness are sometimes met with. The blood pressure may be raised and Wyllie and Schlesinger (1933) have drawn attention to the fact that sufferers from essential hypertension in later life often give a history of migraine, which is, as we know, closely associated with cyclical vomiting.

The duration of the attack is about two to three days, but may be considerably longer. The recovery is sudden and it is of interest to note how often the child himself predicts the onset of his recovery. Death may occur during an attack, more especially in the case of younger children, but this should be uncommon with modern methods of treatment.

The differential diagnosis may be difficult. In excluding acute abdominal conditions a helpful point is that in cyclical vomiting the abdominal wall is unusually slack and hypotonic and the whole abdomen can be palpated with greater ease than normal. Intermittent obstruction due to volvulus of the small intestine may give rise to considerable difficulty in diagnosis.

Cerebral tumour with vomiting, due to intermittent increased intracranial pressure, may be mistaken for cyclical vomiting. The glycosuria which is sometimes present, combined with ketosis and a high blood sugar, may suggest diabetic coma.

Under the same category as cyclical vomiting may be included the child who suffers from motor car or train sickness, or who very readily vomits under any stress or excitement. These children are of a definite type, being thin hypotonic subjects, standing with their pelvis tilted forward and their shoulders rounded. They are, as a rule, rather above the average intelligence, energetic, but tiring easily and taking things rather hard as a whole. They also tend to have sudden attacks of pallor and faint easily.

Recurrent attacks of fever without discernible cause occurring at frequent or regular intervals are probably closely related to cyclical vomiting. It may, however, be argued that all nervous children tend to run a temperature easily, as does, for example, the asthmatic child.

The relationship between migraine and cyclical vomiting is universally recognized, indeed the one frequently merges imperceptibly into the other. The typical adult type of migraine with visual disturbance is not common in the child; more often he has a severe generalized headache, vomits several times, and not infrequently has a rise of temperature.

A connexion between cyclical vomiting and allergy has been suggested, and it has been argued that the attacks are in the nature of a food allergy; alterations in diet and skin tests do not seem to support this view. The fact that a history of asthma and allied disorders is

often found in the family would seem merely to point to the type of stock from which these children come.

The connexion between cyclical vomiting and infection needs consideration. Some would say that infection is always present, and that the child with cyclical vomiting is simply one who shows an exaggeration of the normal tendency of all children to develop ketosis in the presence of infection. Certainly infection may be one of the precipitating causes of an attack, but experience suggests that it is by no means always present.

Finally we must consider whether the cyclical vomiting which we have been considering is really an entity in itself, or if it is just an exaggeration of the normal tendency of all children to develop ketosis, often under very slight provocation. It is, I think, difficult to be certain, but the clear-cut picture of a typical attack, coupled with the frequency and often the regularity of the recurrences, seems to suggest that cyclical vomiting is an entity in itself, with some definite pathology. Greater difficulty, however, arises when we try to link up the typical with the less well-defined manifestations and the allied disorders.

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Professor Stanley Graham (*University of Glasgow*): Cyclical vomiting may be briefly defined as a condition in which there occur periodic attacks of vomiting associated with ketosis. This definition, however, would not be sufficient. The association of vomiting and ketosis is not unusual and does not necessarily imply such a diagnosis unless there are repeated attacks. The first attack therefore raises difficult problems in diagnosis. Abdominal pain is often present and in certain instances may justifiably lead to a diagnosis of appendicitis and operation. Diarrhœa too may be present although it is seldom severe, and in a fairly large proportion of cases pyrexia suggesting the presence of infection ushers in the attack.

Incidence.—The condition seems to be much less frequent than it used to be: certainly the diagnosis is made less frequently. In Victorian days it was regarded as a "bilious attack" and more recently it became almost a fashionable diagnosis masquerading under the label "acidosis". Furthermore, many cases were regarded as acidosis and treated as such with glucose when the true nature of the malady belonged in fact to the realms of psychology. It is not seen much in hospital practice but most frequently in the highly strung, impressionable child of well-to-do and indulgent parents. The sexes are about equally affected. The subject, usually between the ages of 2 and 5 years when the attacks commence, is often tall and spare, of nervous temperament and with mentality above the average. The factors precipitating the attack seem to be emotional upsets and mild infections usually of the respiratory tract.

Clinical features.—The attack may itself be preceded by a day of voracious appetite. Listlessness, yawning, irritability and changes in temperament appear before the vomiting sets in. At this stage, the mother can often anticipate the attack. The vomiting is intractable and may last from a day to four or five days; even sips of water are returned. It is bile-stained and may in the later stages be blood-stained as well. Early in the attack, acetone is present in the breath and in the urine. The child becomes drowsy and dehydrated, lying limply in a state of prostration. At this stage the pauseless acidotic breathing can be readily recognized. Evidence of some infection in the throat or ears may be found in those with a febrile onset but this is seldom troublesome. Abdominal pain perhaps due in some instances to the retching is more often a cause of concern. Cessation of vomiting is followed by rapid improvement or, if the attacks have been occurring for a long time, vomiting may herald an attack of asthma or migraine. A fatal outcome must be very rare. There has not been any fatal case shown in the records of the Royal Hospital for Sick Children, Glasgow.

The attacks may occur several times a year or even monthly, but seldom more often, and after several years may cease or merge into juvenile asthma or migraine. They have not, in my opinion, any special periodicity. The patient, between attacks, enjoys good health and it is curious how often this point is emphasized by the mother.

Biochemical considerations.—Ketonuria in childhood with or without vomiting is a common clinical finding. About 60% of patients in the medical wards of the Royal Hospital for Sick Children, Glasgow, show ketonuria on admission. Formerly it was assumed that ketone bodies were abnormal end-products of fat metabolism and that carbohydrate was required for their complete combustion, i.e. "that fats were burnt in the fire of carbohydrates". The present view is that they are normal products of fat metabolism produced almost entirely in the liver and oxidized in the muscles. Over-production occurs only when the liver glycogen falls below a critical level. The tissues cannot oxidize them nor can the kidneys excrete them beyond a certain rate and the oxidation is uninfluenced by glucose or insulin. When the production of ketones is greater than the tissues can utilize or the kidneys

excrete, the increasing ketonæmia may be a factor in the development of acidosis. Ketosis may therefore be regarded as indicating a diminished glycogen content of the liver and has not necessarily anything to do with acidosis which signifies a diminution in the concentration of hydrogen ions or at least in the alkaline reserve of the body.

In 1906 Naunyn used the word acidosis to describe an accumulation of ketones in the body as indicated by their presence in the urine. In the case of diabetes about which he was writing, the presence of ketones is associated with the presence of both an absolute and relative excess of acid but the impression soon became general that the presence of ketones always signified acidosis. This is not so and such a view has been untenable for many years. Indeed it is interesting to recall that only three years after Naunyn attributed acidosis to excess ketone bodies, L. J. Henderson formulated the basis of our modern knowledge of acid-base balance by stating the three variables concerned, namely, the hydrogen-ion concentration, the free CO_2 and the combined CO_2. Ketonuria can in fact occur either in the presence of excess acid or alkali, and cyclical vomiting associated with a recurring alkalosis has in fact been described.

Biochemical observations during an attack are particularly difficult to obtain. Like juvenile asthma, they rarely begin in hospital, nor can they be induced by a ketogenic diet or acid-producing salts. In addition to the urinary findings, the consistent blood changes are excess of ketones, a low carbon-dioxide combining power and a slight fall in chlorides. This indicates an acid-poisoning or metabolic acidosis (compensated). In severe attacks with air hunger, the pH will be reduced (uncompensated acidosis).

There are observations which suggest that the lowered carbon-dioxide content is the primary change and the vomiting a secondary or compensating mechanism to lose the acid-radicle chloride. Vomiting when primary, as in high intestinal obstruction, produces an alkalosis. It would appear that at certain times under certain conditions there is a sudden call on liver glycogen which when reduced below a certain level produces excess fat catabolism and ketosis.

This fall in liver glycogen may be the result of some emotional upset at home or at school or a mild respiratory infection. It seems unlikely that indiscretions in diet, such as excessive amounts of fried foods, eggs or ice-cream, play any part. The history of the individual case will as a rule enable one to decide on the relative merits of psychological factors and infection in precipitating the attack.

Treatment.—There seems to be some slight justification for giving extra sugar between attacks but for obvious reasons it should not be given as a medicine but along with the diet, although this is apparently of no avail when the precipitating factor occurs. Certainly a reduction in the fat intake is unnecessary and, with rationing in force, unwise. Because these children are often tall and thin, over-anxious mothers may be encouraged to fatten them by giving rich foods such as cream and cod-liver oil. This is equally wrong. All that is indicated is an average mixed diet with extra carbohydrate in the form of sugar. Laxatives, tonics and vitamin preparations should not be prescribed. Even the daily dose of sodium bicarbonate, a favourite remedy presumably because of the tendency to acidosis believed to exist, is of doubtful value. Cyclical vomiting is one of the fairly large group of diseases seen in children in which the parents require as much consideration as the child. The nature of the trouble should be explained to them so that emotional and exhausting factors may be eliminated as far as possible.

Dr. Desmond O'Neill (*Guy's Hospital*): *Recurrent abdominal pain in children.*—In 1948, Dr. R. C. Mac Keith and I decided to carry out, as an experiment, a full examination from both physical and psychiatric aspects of all children attending his clinic with recurrent abdominal pain as a presenting symptom. The purpose of this enterprise was to find how often this symptom, in the children we saw, was the expression of an adaptive disorder: that is, whether the abdominal pain could be one of the somatic signs of emotional tension occasioned by a failure to adapt to particular stresses which the child had to meet. Abdominal pain, in my experience, often has this significance in adults, and we were concerned to find out if it had commonly the same meaning in children. We did our best to establish factual relationships. Our information about the child was derived from outside sources, such as the school, as well as from direct observation in play therapy, and clinical interviews with the child and its parents.

The group which I review contains 25 children. I was able to see all the children with recurrent abdominal pain who had attended the clinic between July 1948 and October 1950, with the exception of one who could not be brought for examination. We kept contact with all the patients throughout this period. The age range was 3 to 16 years; the mean age 8 years. The presenting symptom in all was recurrent abdominal pain for which there was no obvious physical cause. There was much variation in the duration and frequency of attacks: two common sites for the pain were the umbilical zone (12 cases) and the lower abdomen

(7 cases). Severity varied from mild twinges to quite severe spasms, in which the child might double up and become pale. In 7 cases, vomiting occurred in some attacks.

In 4 of our 25 children, the pathogenesis of the pain was quite obscure, and I shall say no more about these. The remaining 21 could be divided into three groups. In the first group of 6, emotional tension was one contributory factor, or determinant, among others; in the second group, of 7 cases, it was probably the main determinant; and in the third group of 8, emotional tension was, in my view, the dominant factor. These results were something of a surprise. Of the 21 children whose attacks were associated in some way with stress, 17 had other tension signs: headaches, poor sleep, bad dreams, fidgets, screaming attacks, tics, stammering, disorders of behaviour, and other similar things. In other words the abdominal pain was in most cases not an isolated symptom, but part of a general syndrome of maladaptation. A history of nervous disturbance or stress disorder was found in one or both parents in 14 cases.

The correlation of attacks of pain with a particular situation was pretty plain in the second and third groups mentioned, i.e. in 15 children. In the first group, of 6, some of the attacks could be traced to this source, and others followed on some physical event, such as having a meal, or had no discoverable cause. Anxiety and fear were much the commonest emotional states associated with the pain, being found in 17 of the 21 cases. In 3, anger seemed to be the most important, and in one, grief. Fear of the teacher at school was noticed in some children: in one small girl, even to sit at home and think about her teacher was enough to set off griping.

I shall mention one illustrative case. A boy of 10 was referred to the hospital because of repeated attacks of central abdominal pain, which had been present for about four months. He described this pain as a sudden stabbing or aching sensation to the left of the navel, which lasted for some minutes. He had on the average 3 attacks a day. In an attack, his face was noticed to be pale. As well as the pain, he had slept badly for six to eight months and had suffered from headaches for two to three years. The boy's father, in his lifetime, was nervous and had severe bilious attacks. David's mother, in speaking of this, said "I wonder if that is connected with David's pain? He remembers it very well". The mother was quick-tempered and rather emotional. David had one brother and two sisters—one nervous, and one who had had an illness diagnosed as "cyclical vomiting", and attacks of abdominal pain. The mother had clearly brought up her children well, but was perhaps a little strict and harsh with them, and then felt guilty afterwards: she was an anxious and hypochondriacal person and communicated her anxiety to them. David was a lively, intelligent, alert, rather sensitive boy. I spent some time with him, and administered two projective tests, the Rorschach and the TAT. I found that he had been sent to a boarding-school for three years at the age of 5, and had suffered a good deal there: he had been bullied and knocked about and felt lonely and miserable. He took his work seriously and felt strongly about it. His mother said that when he had had a bad day at school attacks of pain were likely to follow in the evening; and that he tended to complain of pain when faced with a troublesome lot of homework. I formed the opinion that anxiety could precipitate brief spasms of pain, perhaps large bowel colic, in this boy, and that he sometimes utilized this pain to escape an unpleasant task. After the second visit, he had no more attacks of pain; eighteen months later, he was well and had suffered no return of the symptom. In short, his abdominal pain responded to straightforward psychotherapy and has not so far returned, in spite of the fact that there was so strong a family history of predisposition to this kind of illness.

Where emotional tension was thought to be an ætiological factor, I did my best to modify the environment, or the child's attitude to it, or both. In young children, play therapy, and in older children, brief psychotherapy was employed. In a few cases, the causal situation had been changed by some outside agency while the child was under observation, with consequent disappearance of the attacks. I was able to treat 16 children at some length. In 3 the symptoms went on as before; 6 were improved; and in 7 the attacks of pain cleared up, and the child seemed generally better. I was able to verify in many children our hypotheses about the origin of the pain; for example, the attacks diminished considerably in one child directly after she had begun to show violence to the puppets at play therapy, and to do to them what she would have liked to do to her own parents.

I am well aware that there are many sources of possible error in this field; in this note, I have given the findings as they appeared to me. To sum up, out of 25 consecutive cases of recurrent abdominal pain seen in an outpatient department, at least 15 showed clear signs of an emotional disharmony which was causally related to the pain: our evidence for this claim is, first, the nature of the syndrome of which the pain was one element; second, the time relationships of the pain; and third, the effect of treatment aimed at relieving the underlying tension state. It would appear that this syndrome is not an uncommon condition.

Many problems are raised by this conclusion, of which I will mention one: the problem of why these children react to stress with abdominal pain, and not with some other symptom. We can find some clue to this difficult question in the family history. Of the 21 cases I mentioned above, there were 14 in which one or other parent, or both, had dyspeptic symptoms: abdominal pain in 9, "indigestion" in 4, and duodenal ulcer in one. This may point to the genetic transmission of some local fault or vulnerability, or in some at least another mechanism

may be concerned—that of identification. I made a practice of keeping pain charts with the location of the pain marked in by the patient himself; in several cases there was a quite striking similarity between the patient's own chart and that drawn by the mother to describe her own pain.

Dr. **R. E. Smith** (*Consulting Medical Officer, Rugby School*): *Prognosis.*—The outlook in the majority of sufferers is excellent, but fatalities do occur. Those with greater experience of younger children should tell us whether intravenous glucose therapy improves the prognosis in those very severe cases. Prognosis in the majority depends on accurate diagnosis and the danger is greatest when the child who is an habitual vomiter gets some other trouble, particularly appendicitis. Certainly acidosis and appendicitis can occur together, and if there is any doubt it is wise to have the appendix out. On several occasions the surgeon has volunteered the statement that the appendix was worse than he expected, although before operation he had said: "It will probably settle down, but it is best to be safe". The child with acute appendicitis who also has acidosis is less liable to develop rigidity. I have also had one boy who had pyloric stenosis and because he had previous vomiting attacks, I had great difficulty in getting his parents to take note of his new type of vomiting, which was copious and required intravenous therapy. He had no recurrence after gastro-jejunostomy. The surgeon thought the stenosis was due to a healed pyloric ulcer.

My experience has been chiefly confined to adolescents at Rugby School where one of the strictest rules is that any boy who has abdominal pain or vomiting must be seen by the medical officer at once. I shall make a few observations on the history of some 700 boys, aged 13 to 18, to try and answer the questions:

(1) What is the chance of the child growing out of acidosis in adolescence?
(2) What are the sequelæ?
(3) What is the prognosis of the sequelæ?

All the new boys were asked if they had had attacks of vomiting; 402 said "No". A parent, however, would sometimes say that the child had had acidosis, &c., but the boy had honestly forgotten. 102 said "seldom" or "very rarely"; 198 said "occasionally", "sometimes", "often", and on a few occasions "with headaches".

88 of these 702 had 93 attacks, i.e. 10 attacks in boys aged 13; 35 aged 14; 24 aged 15; 10 aged 16; 13 aged 17; one aged 18; as well as two boys who had at least one attack in every year at school. There is approximately an equal number of boys aged 14, 15, 16 and 17, and there is obvious decline in incidence around 16 and 17. There are fewer boys aged 13 than 14 in the school, the age of entry being 13 plus. Acetone was present in the urine of 75% of those aged 13; 60% of those aged 14 and 15; 50% of those aged 16; 61% of those aged 17.

Many of the 198 with a previous history qualified their answer by some such phrase as "When I was young", or that attacks stopped at 10 or at 12. Of those 198, there were 49 who had further attacks, i.e. 25%. I would like to emphasize that, during the same period, 39 of the remaining 500, i.e. 8%, who had never or seldom had attacks, had what was apparently their first attack, e.g.:

H. H., aged 13½, felt heavy over his forehead on November 11, 1942. Temperature 100° F. rising to 103° F. next morning and then by lysis to normal in thirty-six hours. Acetonuria ++++. On November 12, acetonuria +++ and he vomited once at 20.00 hrs.

The intervals in the others were often long.

E. M., aged 17, complained of headache and was thrice violently sick. Temperature rose to 101° F. Acetone ++. Last attack seven years previously.

Equally, attacks may apparently end at any age, e.g.:

J. E., who had had attacks approximately every six months had one attack of acidotic vomiting at age 14, and no more while at school.

Therefore the answer to the first question is that approximately a quarter of those boys who had vomiting attacks are still liable to have them infrequently during adolescence and that even a few of those who have forgotten or never had attacks may suddenly have one.

Thirteen of those who had had vomiting developed migrainous headaches sufficient to warrant their consulting me. My statistics are not good enough to say whether this is a significant figure and I have no control series. Therefore I cannot answer question 2 accurately, but certainly treatment for acidosis, &c., has little effect upon migraine.

The most dramatic migrainous sequel is epilepsy. One boy who had habitual and often violent sick headaches suddenly had a severe epileptic fit in the school library. He was treated with sedatives and had no further attacks, although, as Ryle (1948, Natural History of Disease. Lond., p. 387) records, attacks may recur. The only other boy who crossed the frontier from migraine to epilepsy continued to have attacks. His father, a well-known surgeon, had had similar attacks until aged 17, during which he often lost consciousness, and a paternal aunt had similar attacks. Therefore, the father was against luminal. The boy

continued to have attacks, but from 1939 to 1943 had only 4; in 1944 these became more frequent, which he attributed to working about 60 hours a week at a desk; in 1945 he had 40 attacks, and in 1946 20 attacks. Then he found that if he did not overwork and had sufficient sleep, and kept his bowels regular, he reduced the attacks, and from 1947–50 he has had an average of 1 attack every three months, for which he takes 2 luminals and has a day in bed after each attack.

The majority of cyclical vomiters "grow out of it".

Dr. R. C. Mac Keith observed that when attacks were associated with an emotional disturbance there might be a lapse of time of about forty-eight hours between the emotional shock and the onset of symptoms.

Dr. J. P. M. Tizard drew attention to some of the organic diseases involved in the differential diagnosis of cyclical vomiting. He considered that abdominal pain was *not* a prominent symptom of cyclical vomiting and, if severe or if preceding the vomiting, should certainly arouse the suspicion of appendicitis or other organic disorder. Organic diseases characterized by recurrent vomiting, but often *without* severe abdominal pain, included the common conditions of tonsillitis and pyelitis, but also the rarer congenital œsophageal anomalies and upper intestinal obstructions. He quoted the case of a child who had suffered from recurrent duodenal obstruction due to a congenital membrane. In this case the erroneous diagnosis of cyclical vomiting had been made.

Dr. Hugh Jolly also emphasized the diagnostic difficulties and described a case of lead poisoning in which a diagnosis of cyclical vomiting had been entertained for some time before the true diagnosis was made.

Dr. J. J. Kempton wished to join with Professor Graham in deprecating the use of the word "acidosis" in speaking of the recurrent bilious attacks of childhood.

In the older textbooks—Still and Hutchison—there were descriptions of these symptom complexes, not as separate conditions, but as occurring in states of general ill-health, and there was still much to be said for this: so often these symptoms appeared, or were accentuated against a background of mild illness such as that of chronic upper respiratory infection, and if the general health of the child was improved the attacks tended to become less frequent and less severe.

Professor Alan Moncrieff said that cyclical vomiting was not a condition *sui generis*. Ketosis could not be held to be the primary cause. In observations on children on ketogenic diets for epilepsy in whom ketosis was manifest, he had not seen a single case in which an attack of vomiting had occurred, though transient nausea had been recorded. He regarded infection as playing an important part in the ætiology and thought that the blood chemistry of these children was undoubtedly labile. He had seen tetany caused in one such child by giving sodium bicarbonate too freely. In the treatment he laid the greatest emphasis on rest during the day, lying down, and regular doses of phenobarbitone. While admitting the value of Dr. O'Neill's researches into the psychological background he was not at all ready to accept the conclusions offered without a similar study of a control series. There were many traps in diagnosis and every case demanded a search into the possibility of infection, organic cause and psychological cause.

Dr. W. W. Payne began by quoting his earlier (unpublished) work on sugar tolerance curves in children with periodic vomiting. The sugar tolerance curve he found to be normal. The adrenaline response was rather higher than normal and the lævulose tolerance curve was higher than normal. At the beginning of an attack the blood sugar is raised. Later it is low on account of starvation. He described a periodic syndrome with the following features: Abdominal pain, pallor, headache, nausea and sometimes vomiting, the explanation of the symptoms being as follows: Excessive utilization of blood glucose by nervous highly strung children; low glycogen stores in the liver; hypoglycæmia; excessive adrenaline secretion in response to hypoglycæmia; gastric stasis in response to the adrenaline; further fall of blood sugar and further adrenaline secretion. The symptoms, abdominal pain, pallor, headache and vomiting were due to the adrenaline. He had seen diabetic children who had been treated with adrenaline for hypoglycæmia occasionally suffer from these symptoms. Treatment: suprarenal activity being the chief factor, he recommended continuous sedatives and sugar at intervals throughout the day.

Dr. G. M. Kerr said that general practitioners preferred the term "bilious attack" to cyclical vomiting, which was both difficult to pronounce and difficult to spell and added little to clarity. He stated that the condition appeared to be no less common to-day than two decades or more ago when it received much attention from the children's physicians. The reason why it was less the concern of the pædiatricians to-day was that the general practitioner knew how to treat it. The points he emphasized in treatment were the giving of glucose freely (this not only helps the child but appeals to the mother who likes to feel

she is feeding her child) and rectal nembutal, which was very effective, provided the rectum was, as he put it, "with you".

Dr. **J. T. Edwards** described bovine acetonæmia, the only difference between this condition and cyclical vomiting of children apparently being the anatomical formation of the cow's stomach which makes vomiting an impossibility. Cows do, however, suffer from eructations, ketonuria and wasting. In dogs in highly selected stocks, whom he compared to nervous children, it was a common practice to wean puppies early for sale purposes and feed them on cow's milk. States of ketosis were commonly seen in these young dogs. Allergy to cow's milk was also, he thought, a possible explanation here.

The **President** spoke of the similarity of some periodic attacks of abdominal pain to cyclical vomiting. He had no quarrel with the term "abdominal migraine" for these attacks.

Professor Stanley Graham, in reply to a question, said that in his experience, among the sequels to cyclical vomiting in later childhood, juvenile asthma was more common than migraine. The latter appeared more frequently in adult life.

[*February* 23, 1951]

Osteochondrosis of the Tibia.—W. L. CALNAN, M.D.

Edward G. (12.7.48).

Third child of healthy parents. Full-term normal birth. Birth-weight 8½ lb. Breast fed three and a half months. Received adequate cod-liver oil from birth. Father and two other children had bow legs in early childhood.

Bowing of legs, first noticed at age of 8 months, increased up to age of 18 months. He stood at 10 months, walked at 14 months.

On examination.—Healthy, well-developed boy with bow legs. No clinical evidence of rickets.

X-ray tibiæ, 13.6.50 (Fig. 1): Lateral bowing of the upper half of both tibiæ. "Beaking" of the medial aspect of the upper end of the shaft with fragmentation and some increase in density.

12.2.51: Healing of the proximal tibial diaphyses.

Blood Wassermann and Kahn reactions negative.

Serum alkaline phosphatase (26.7.50) 34 K. A. units, (17.11.50) 43 K. A. units.

Serum inorganic phosphorus (17.11.50) 2 mg. per 100 ml.

FIG. 1.—"Beaking" of the medial side of the upper end of tibia with fragmentation.

Serum calcium (17.11.50) 11·4 mg. per 100 ml.

The boy shows the features of the infantile type of osteochondrosis of the tibia or tibia vara (Blount, W. P. (1937) *J. Bone Jt. Surg.*, **19**, 1). Spontaneous correction of the deformity occurs in many children; splinting and surgical interference are seldom required. Pathologically, the condition shows similar features to the other osteochondroses (Osgood-Schlatter, Kienböck, Perthes, Köhler, &c.) which have been attributed to aseptic focal necrosis.

Two further examples of the condition have been seen at the same hospital during the past year.

Sexual Precocity Following Recovery from Tuberculous Meningitis with Hydrocephalus. Calcifying Intracranial Tuberculoma. Cerebral Cyst. Optic Atrophy with Good Vision.—J. LORBER, M.B., M.R.C.P. (by permission of Professor R. S. ILLINGWORTH, M.D., F.R.C.P.).

W. M., female (16.8.43).

History.—May 4, 1949: Admitted hospital having been in coma for two days. Tuberculous meningitis confirmed by recovery of tubercle bacilli of human type from the C.S.F. X-ray chest: Right hilar mass. X-ray skull negative.

Family history.—No known sexual precocity. Mother and maternal aunt started menstruating at 16 years old.

Treatment and progress.—Intramuscular streptomycin, May–November 1949 (20 mg./lb., 44 mg./kg.). Intrathecal streptomycin, May–August 1949; Sulphetrone (orally), May–December 1949. Remained unconscious for two months, with wasting and bedsores.

21.5.49: Pneumo-encephalogram: moderate hydrocephalus. Tentorial block. Incipient optic atrophy; dilated fixed pupils.

14.6.49: Spinal block.

20.6.49: Ventriculogram: Grossly increased hydrocephalus; cyst in right frontal lobe. Increasing optic atrophy. Spinal block resolved.

July 1949: Recovery of consciousness. Contractures of hips and knees. Rapid improvement in mental condition, continued wasting.

7.9.49: Sitting up, very well and intelligent. Weight 36 lb.—the lowest weight. Pneumo-encephalogram: Further increase in hydrocephalus, frontal lobe cyst persisting. Complete optic atrophy.

Further progress uneventful. Contractures of hips and knees no longer detectable after February 1950.

January 1950: Persistent optic atrophy. Vision: L. 6/24; R. 6/12. Fields restricted.

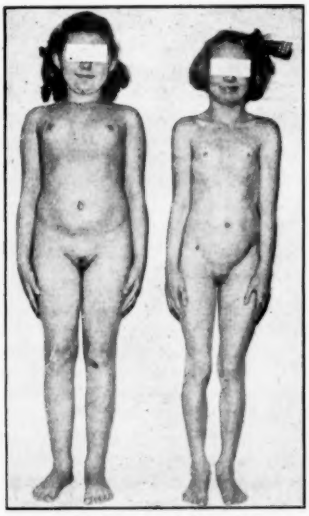

FIG. 1.—Patient (on left) at the age of 7 years, together with normal control, aged 9½ (on right).

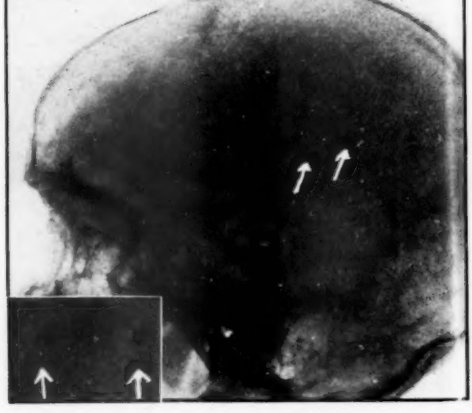

FIG. 2.—Radiograph of skull, lateral view, showing two calcified shadows on the right side. Inset shows the lesions to have an irregular round periphery and a clear centre.

February 1950: Infective hepatitis, quick recovery.

April 1950: I.Q. = 100 (Terman-Merrill).

September 1950: (Aged 7 years.) Breast and pubic hair development beginning.

November 1950: Considerable breast and pubic hair development. External genitalia of adult type. No menses. Wt. 72 lb. Ht. 4 ft. 3 in. Some hearing loss in speech range. X-ray skull: 2 centres of calcification in the right parietal lobe.

December 1950: Glucose and insulin tolerance tests normal. Bony age: approximately 9 years.

January 1951: Menarche.

February 1951: Aged 7½ years. In excellent health. Second menstrual period. No change in physical signs. Weight: 76½ lb. (equals mean for age 10¾). Average for age 55·2 lb. Height: 52 in. (equals mean for age 9). Average for age 49·3 in.

Comments.—It is common knowledge that tumours in the region of the third ventricle and the hypothalamus may lead to precocious sexual development. Much less often has precocity been observed in hydrocephalus of inflammatory origin. Most of the reported cases followed acute meningitis in infancy and the appearance of secondary sexual characteristics was usually delayed for several years. Schlesinger (1935) showed a girl at a meeting of this Section seventeen years ago. This girl had post-basal meningitis at 4 months of age and recovered with residual hydrocephalus, spasticity, optic atrophy and mental deficiency. Sexual development started at 7 years of age but she had not menstruated. Similar cases had been reported by Moniz and Lima (1932), de Cardenas (1932) and Dorff and Schapiro (1937). André-Thomas and Schaeffer's patient was a 12-year-old boy in whom gross distension of the third ventricle with destructive lesions of long standing were found in the tuber cinereum and hypothalamus at autopsy. In all these cases gross mental and physical defects were associated with the sexual precocity. Menstruation occurred only in one 9½-year-old girl.

In 1935 Poos described a boy of 7 who was diagnosed as suffering from chronic tuberculous meningo-encephalitis and who had symptoms of precocious sexual development before his death. At autopsy tuberculous lesions were found in the walls of the third and lateral ventricles. Lincoln *et al.* (1948) reported precocious breast development in a 2-year-old girl treated with Promizole for miliary tuberculosis. They attributed this to the toxic effect of the drug, but it appears likely that a tuberculous lesion in the region of the hypothalamus was responsible for this development, as was pointed out by Wilkins (1950). This patient had no meningitis or hydrocephalus.

In the recent vast literature on tuberculous meningitis I have not been able to find a report of sexual precocity occurring in recovered children. Obesity, which is thought to be of cerebral origin, has, however, been frequently observed.

This case shows a combination of apparently unique features.

She is sexually fully developed at the age of 7½, a year after recovery from tuberculous meningitis (Fig. 1). This sexual development appears to be connected with a considerable degree of hydrocephalus which has been demonstrated by serial encephalograms. There was no evidence of regression of the hydrocephalus on the last encephalogram performed at a time when she was well on the way to recovery.

Like several of the previously reported cases after pyogenic meningitis, she has optic atrophy, but her vision is good. Unlike all other cases, however, she is physically and mentally a perfectly healthy girl pursuing activities suitable to her age. Her interests are those of a girl of 7 years.

The last unusual feature in this case is the appearance of intracranial calcifications (Fig. 2) eighteen months after the onset of the meningitis. These lesions are considered to be calcifying intracerebral tuberculomata. Although these have been described in the past, they are but rarely found (Weens, 1948). This is the first case among the many recoveries in my experience.

It may be contended that her precocity is merely a physiological variation of the normal. This is possible, but the coincidence with post-meningitic hydrocephalus and calcifying lesion in or near the wall of the third ventricle appears to be strong evidence that this is not so. There is no family history of early sexual development.

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Dr. Hugh Jolly considered that the sexual precocity was more likely to be due to tuberculomata in the hypothalamus rather than the associated hydrocephalus. In a survey of sexual precocity he had been unable to trace any report of the condition associated with congenital hydrocephalus, and stated that involvement of the hypothalamus was necessary for the development of sexual precocity in cases of organic cerebral disease.

Acute Dermatomyositis Treated with ACTH.—B. SCHLESINGER, O.B.E., F.R.C.P.

Sally D., aged 10 years.

Admitted on November 21, 1950, with an eight weeks' history of erythema of the face of butterfly distribution followed by tender œdema of the underlying subcutaneous tissues; a similar œdema of the subcutaneous tissues of the limbs then developed, which was most marked on elbows, hands and ankles. Also gradual diminution of power in all the skeletal musculature and increasing stiffness.

On admission she had a mild pyrexia; there were enlarged capillary loops in nail beds and on gum margins, and erythematous patches on the buccal mucosa. There was limitation of movement of joints, most marked in the elbows, shoulders and neck, and absent in joints of hand and foot.

Muscle biopsy: Degenerative changes with some reactive cellular infiltration. There was a trace of albumin in the urine. W.B.C. count normal.

After fourteen days' observation, ACTH was given for a period of thirty-six days (40 mg. a day for twenty-three days, given six-hourly, followed by 30 mg. a day for eleven days, 15 mg. a day for two days given eight-hourly) with 3 grammes potassium chloride daily and a low salt diet. Physiotherapy was given throughout.

Clinical improvement began within a few hours of the start of treatment, with diminution in all the symptoms and a gradual loss of œdema; the weight fell 8½ lb. in three weeks, and she became afebrile. The creatinine excretion rose from 7·9 mg./kilo per twenty-four hours to 10·8 mg./kilo under treatment, while creatine excretion remained constant round about 3·9 mg./kilo.

Within twenty-four hours of the cessation of treatment, all the symptoms began to return, and she put on 6 lb. in weight in five days.

After an eleven-day interval, treatment with ACTH was recommenced in a daily dosage of 30 mg. Symptoms and œdema diminished as before.

Generalized Sarcoidosis with Renal Involvement.—M. K. KEECH, M.D. (for R. LIGHTWOOD, M.D.). (*See also* PRITCHARD, P. M. M. (1950) *Proc. R. Soc. Med.*, **43**, 236.)

J. S., girl born February 1945.

1948—May: Puffy eyes treated as angioneurotic œdema with Benadryl. July: Acute tonsillitis, treated with Sulphamezathine. October: Miserable, poor general condition, losing weight, pyrexial; generalized eruption of flat polygonal papules surmounted by minute vesicles. The eruption was chiefly on trunk and upper limbs and persisted eight months. November: Biopsy of skin: No definite diagnosis, ? periarteritis nodosa.

1949—January: General condition worse, tachycardia, raised B.S.R., hepatomegaly. Increasing heart size and bilateral small pleural effusions responded to digitalis. Given penicillin, sulphonamide and calciferol. March: Spleen palpable. Albuminuria. Skin lesions gradually faded, leaving puckered scars. June: Heart block lasting five days. August: Blood pressure found to be persistently 165/120. October: Retinal œdema (right). *Muscle biopsy*: Paravascular granulomatous lesions with giant cells of Langhans' type (Fig. 1). Shown to this Section (reference above). November: Retinal œdema worse; uveitis (left) with posterior synechiæ and K.P. Blood pressure 170/132.

1950—June: Pale, anæmic; photophobia, bilateral iridocyclitis, lymphadeno-hepato-splenomegaly, hypertension 260/160, large heart, aortic diastolic and variable mitral diastolic murmurs, pinhead pigmented scars of trunk. Maintained pyrexia to 100 or 102° F., progressive deterioration of eye condition. *Biopsy liver and voluntary muscle*: Nodules of sarcoidosis (Fig. 2); biopsy spleen: severe arteriolar hyalinization. On review of the previous muscle and skin sections, it was considered they could also be interpreted as sarcoid lesions. October: Rash for one week of palpable painless nodules, ⅛ in. to ¼ in. diameter, chiefly on lower limbs and leaving no scars. *Biopsy*: Cutaneous sarcoid (Fig. 3).

Investigations.—Blood urea (April 1949, June 1950) normal. 57 mg.% in September 1950. I.V.P. (September 1949, July 1950) normal. Urine concentration poor. Highest sp. gr. 1010. Albuminuria 100–300 mg.%. Granular and hyaline casts appeared February 1951. Serum protein (June 1950) 7·7 grammes: alb. 5·6 grammes, glob. 2·1 grammes %. Serum calcium raised (11·4–14·2 mg.% September–November 1950). Serum phosphorus and alkaline phosphatase both normal. Congo red test negative. X-ray bones: No sarcoidosis.

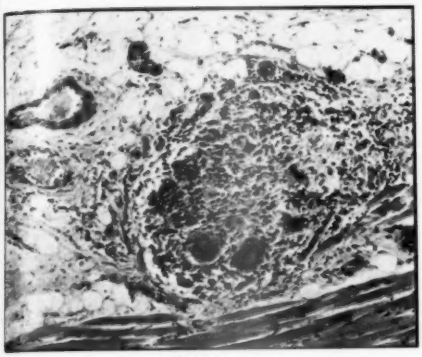

FIG. 1.

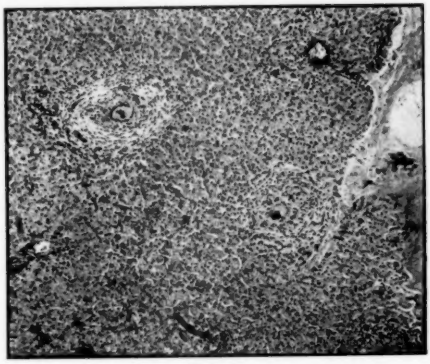

FIG. 2.

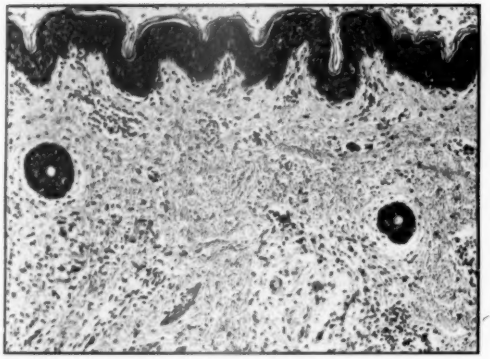

FIG. 1.—Voluntary muscle. (H. and E. × 94.) Paravascular granuloma with giant cells of Langhans' type. Blood vessels normal.

FIG. 2.—Liver. (H. and E. × 94.) Several miliary granulomata in the parenchyma and portal tracts characteristic of sarcoidosis.

← FIG. 3.—Skin. (H. and E. × 94.) Two typical tubercle-like nodules of sarcoidosis.

X-ray chest: Heart large, lungs clear. Mantoux 1/100, five times in two years, all negative before October 1950. Tuberculin neutralizing factor (Wells and Wylie, 1949) present in serum.

Recent treatment.—Summer 1950: Streptomycin for one month. October 1950: B.C.G. vaccination. Local reaction fifteen weeks later with positive Mantoux in seventeenth week. Calciferol (for sarcoidosis, iridocyclitis; Scadding, 1950) abandoned because of high serum calcium before treatment started. Cortisone locally to the eyes had no effect on permanent inactive lesion. Hexamethonium bromide did not affect the blood pressure. Iron did not affect the anæmia.

Present condition.—February 1951: Cheerful despite pyrexia, tachycardia, anæmia and raised B.S.R. Blood pressure 180/120–200/140; albuminuria; heart murmurs unchanged. Quiescent iridocyclitis, severe keratopathy, exudate in macular region right fundus oculi.

Comment.—A proven case of generalized sarcoidosis with renal involvement causing hypertension and possibly endocardial involvement. Only one case of sarcoidosis with hypertension (Rotenberg and Guggenheim, 1942) is reported. High serum calcium, common in sarcoidosis, is present but the usual hyperglobulinæmia is absent.

Dr. P. M. M. Pritchard made an apologia to the meeting for presenting this case as ? Periarteritis nodosa in October 1949, but pointed out the non-specific histological findings of the original skin and muscle biopsies. The characteristic later biopsies clarified the position, and review of the earlier sections showed they were all the same disease. He also emphasized that Mantoux-neutralization (Wells and Wylie, 1949) was not a specific test for sarcoid; it occasionally occurred in normal people and other diseases.

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Hepatosplenomegaly with Neutropenia.—F. W. NASH, M.D. (for KENNETH H. TALLERMAN, M.C., F.R.C.P.).

Michael M., aged 2 years 11 months.

Family history.—Only child. Both parents well. Father had malaria in the Army. No history of anæmia or jaundice in family. No Mediterranean ancestry.

Past history.—Normal development. Never abroad. Previously healthy apart from acute otitis media two years ago, measles one and a half years ago, and epistaxis (following injury) three months ago. September 26, 1950: Admitted to another hospital with *one week's history* of listlessness, fever and vague pains in the legs. He had been treated at home as a case of pneumonia with sulphathiazole 9·0 grammes in three days. *On examination*: Spleen 1½ in. below ribs; liver just felt; no enlarged glands; intermittent pyrexia up to 105° F. Treated with penicillin I.M. with slight improvement, although the liver and spleen became larger and the pyrexia persisted.

On examination (October 25, 1950): Ill child. T. 100·2° F. Moderate pallor. Sallow, not jaundiced. Lymph glands normal. Liver 2¾ in., spleen 2¾ in. below costal margin. Other systems normal. No cause found for the pyrexia.

Progress.—Throughout his illness he has had episodes of irregular pyrexia (up to 105° F.) which have subsided only within the last two weeks. Many of these febrile periods were associated with pyogenic infections, viz. pulp infection of thumb and axillary abscess; skin pustules; abscess of buttocks; conjunctivitis; bilateral otitis media (two attacks) persisting in subacute form on the right side; purulent rhinitis; recurrent pharyngitis. Various organisms have been isolated, chiefly *Str. hæmolyticus* and *Staph. pyogenes*. All were penicillin sensitive in spite of long-continued treatment with this drug, both parenterally and locally. Following right cortical mastoid operation on 16.1.51 his general condition has improved considerably. In view of persistent rhinitis and evidence of infection of antra, the tonsils and adenoids were removed on 12.2.51. The liver and spleen have not enlarged appreciably during the past three months.

Investigations.—Blood picture: Rh negative. Normochromic anæmia (Hb 60 to 70% Haldane). Reticulocytes usually 2 to 4%, once 7%. Occasional normoblast in peripheral blood. W.B.C.: Total usually less than 6,000 and polymorphs less than 1,500/c.mm. Lowest, 1,800 (polymorphs 240)/c.mm. Highest, 8,900 (polymorphs 3,300)/c.mm. Platelets normal apart from two readings of 50,000 and 77,600/c.mm. No malarial parasites in blood smears. Red cell fragility normal. Blood cultures (2) sterile. Serum agglutinins (enteric and abortus group) negative. Paul-Bunnell, direct Race-Coombs, W.R.—all negative.

Marrow: Aspiration and histological sections of biopsy specimen—normoblastic reaction with normal leucopoiesis. Special stains show no excess of free iron.

Liver function tests:	1.11.50	14.12.50	11.1.51	11.2.51
Bilirubin mg.%	0·8	3·8	0·5	—
Alk. phosphatase (K.A. units) ..	37	22·5	27·0	—
Thymol turbidity	4·5	8·6	13·1	12·7
Cephalin cholesterol flocculation	0	1·0	2·0	—
Serum colloidal gold	0	0	2·0	—
Plasma protein g. % (Alb.) ..	4·2	3·0	3·6	—
(Glob.) ..	2·4	2·6	2·8	—

Urine: Several specimens (qualitative, microscopy and culture) normal. Excess of urobilin, bilirubin and bile salts present on two occasions.

Stools: No occult blood. Fæcal stercobilin: 67 mg./twenty-four hours.

X-rays: Whole skeleton normal except for evidence of sinus and mastoid infection.

Liver biopsy (12.12.50): Patchy, chronic, non-specific inflammation around portal systems. Well-preserved hepatic parenchyma. No retention of bile.

Mantoux test (1 : 1,000): Negative. Histoplasmin skin test: Negative.

Comment.—The chief points of interest in this case are the presence of persistent neutropenia, hepatosplenomegaly, and evidence of progressive impairment of liver function. It has been suggested that the child might be suffering from Banti's syndrome. If this refers to a series of disorders more commonly seen in adults and grouped together as examples of congestive splenomegaly, then this patient shows certain atypical features; in particular the rapid onset and febrile course. However, there is little doubt that he is suffering from a progressive hepatitis of obscure ætiology, and the enlargement of the spleen is possibly secondary to this. As yet, the symptoms have been entirely related to intercurrent infections and these are, of course, the natural result of a persistently low neutrophil count.

The association of enlargement of the spleen with chronic neutropenia and a normal or

hyperplastic marrow reaction has been regarded as one variety of hypersplenism. (Wiseman and Doan, 1939, 1942.) There are now on record several cases of neutropenia in which splenectomy has resulted in a permanent return of the W.B.C. count to normal and cure of the patient.

Apart from these instances of so-called primary hypersplenism, it is clear that many diseases which involve the spleen secondarily may also be associated with severe neutropenia. Examples are: Hodgkin's disease, Felty's syndrome, Gaucher's disease, sarcoidosis, malaria and kala-azar (Dameshek, 1946; Scott, 1949).

Removal of the spleen in this group of cases, although rarely indicated, is sometimes effective in restoring the blood count to normal.

We suggest that the neutropenia in our patient is an example of secondary hypersplenism although we are unable to explain the ætiology of the original involvement of liver and spleen.

If this child suffers a recurrence of pyogenic infections then splenectomy would be a reasonable procedure. It is hoped that this would result in a significant increase in the W.B.C. count; but one would not expect an improvement in liver function, and it might be wise to consider performing some form of porto-caval anastomosis at the same time.

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Dr. E. P. Quibell referred to his own experience of a similar case and the use of oral extracts of bone-marrow which he felt had been of some value in correcting the neutropenia.

Dr. Duncan Leys suggested that the improvement on admission to hospital might be due to correction of a nutritional deficiency.

Congenital Ptosis with Jaw-winking.—R. MAC KEITH, D.M.

John K., aged 13 years, with migraine and other recurrent symptoms and a left ptosis since birth. As an infant at the breast, his left eyelid was seen to lift when he moved his jaw. The Marcus Gunn phenomenon occurs when his jaw opens or moves to the right or forward.

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Congenital Cranial Nerve Palsies and Deformity of Little Fingers.—R. MAC KEITH, D.M.

Lance B., aged 9 years. Birth-weight 7 lb.; feeding difficulty attributed to receding chin, immobile tongue and inability to close mouth—all present from birth. At 6 months he was in hospital with severe vomiting; sent home as "hopeless" he recovered rapidly except that a squint was present. At 18 months he had pertussis with fainting from coughing spells. He has had three operations for correction of the squint. He has asthmatic bronchitis. His intelligence is normal. On examination he has a bilateral abducens, bilateral facial and left hypoglossal nerve palsy and radial deviation of the terminal phalanx of the fifth digit of each hand. He presents a well-recognized picture, for congenital facial diplegia is usually associated with abducens palsy and frequently with other cranial nerve palsies and other deformities such as absent pectoral muscles, clubfoot and poly- or syndactyly, &c.

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Chondro-ectodermal Dysplasia (Ellis-Van Creveld Syndrome).—S. D. V. WELLER, M.D., M.R.C.P. (by permission of W. G. WYLLIE, F.R.C.P.). (Cf. (1940) *Arch. Dis. Child.*, **15**, 65.)

S.O., aged 2 (girl).

Family history.—Paternal grandfather had extra digit on right hand and right foot. Parents normal (Turkish): no consanguinity. Elder sibling normal.

Past history.—Normal pregnancy and delivery: birth-weight unknown. At six months weighed 7 lb. Slow development: two attacks of pneumonia. Walked at 23 months. Speech just starting.

Present condition:—Weight 16 lb. Height 30 inches. Skull circumference 17 inches. Probably mentally backward. Defects presented are:

(1) *Ectodermal dysplasia*: Involving nails, teeth, sparse hair. This may be related to the appearance of the upper lip, which looks as if the median part was less developed than the lateral parts, giving a suggestion of hare-lip.

(2) *Chondrodysplasia*: Causing *dwarfism*, with limbs disproportionately short. X-rays show short and broad "long" bones, partial fusion of carpal bones, ill-developed terminal phalanges, and dysplastic epiphyseal development in several proximal phalanges (Fig. 1).

FIG. 1.—X-ray of hands showing polydactyly, giant carpal bone (L. wrist) and pyramidal or "bottle base" defect in proximal ends of shafts of phalanges.

FIG. 2.—Photograph of hands showing polydactyly, dystrophic nails and stiff fingers.

(3) *Congenital morbus cordis*: considered to be an atrial septal defect. This may (or may not) be related to the *large liver and spleen* and to the dwarfism. Sail shadow in left chest considered to be thymic (present since six months).

(4) *Polydactyly*: Feet are short and broad, with a broad fourth toe, and toes look twisted. Hands are large relative to arms: six digits on each hand: extra digit on left hand is bifid (Fig. 2).

(5) *Arthrogryposis of interphalangeal joints* of all fingers. The degree of fixation is not constant, but all joints are affected.

It was considered that these five features represent the complete syndrome. Of the cases described by Ellis and Van Creveld, all showed only four of the five features.

Exophthalmic Goitre without Hyperthyroidism.—S. D. V. WELLER, M.D., M.R.C.P.

Christine A., aged 8.

Family history.—Nil relevant.

Past history.—Always had rather puffy eyelids.

Present illness.—Since April 1950, tendency to staring eyes, nervousness, irritability, sleeplessness and loss of weight. All symptoms aggravated after tonsillitis in November 1950, but improved after Christmas.

6.1.51: Referred to Children's Clinic: found to have exophthalmos (right 16 mm., left 17·5 mm.), lid lag, poor convergence. Lateral lobes of thyroid large, but isthmus normal. Pulse slow. No tremor or nervousness.

Investigations.—

B.M.R.	Upper limits of normal
Bone age	
Radioactive iodine uptake and retention	
Blood protein bound iodine	
Blood cholesterol	146 mg.%
Blood count	Normal
Urine	
X-rays of chest and pituitary fossa	
Blood ergothioneine	Nil

Progress.—The thyroid enlargement and eye signs are tending to regress. No treatment has been given.

This was considered to be a case of Graves' disease in which the ophthalmopathic signs predominated, and in which spontaneous recovery was occurring—an extremely rare event. Eye signs were, however, still detectable, while clinical and biochemical evidence of hyperthyroidism was no longer present.

Calcified Aneurysms of the Coronary Arteries.—J. J. KEMPTON, M.D., M.R.C.P., D.C.H.

Sheila B., aged 9½ years.

Until her death the child had been well and active. She died suddenly while playing hockey on October 4, 1950.

Parents and two other children are healthy, and her birth and early development were normal. There were no serious illnesses until the age of 4½, when she was admitted to the Battle Hospital, Reading, with a febrile illness commencing with a sore throat. There were some enlarged cervical glands, and she had a temperature of 101° F. to 105° F. for five days. There is no record of any detailed investigation, but she was considered to be a case of septicæmia and was given penicillin, three-hourly, for twelve days. She was discharged from hospital quite well at the end of a month, and had no further illnesses of significance until her death. Examination by the school medical officer at the age of 5½ revealed no abnormality.

Post-mortem examination showed nothing abnormal apart from the heart. The kidneys, the renal and mesenteric vessels, and the arteries at the base of the brain were normal.

The heart shows considerable myocardial fibrosis confirmed by histology, and two large calcified aneurysms of the main coronary arteries. The left coronary artery is opened and leads into one aneurysm. The right coronary artery is occluded near the other aneurysm. The valves and great vessels are normal. The opened aneurysm has a hard, calcified, laminated wall with a central mass of old blood clot. Death would appear to have been due to a massive occlusion of the right coronary artery.

Coronary artery aneurysm is a fairly well-known rarity, about 60 cases having been reported since Bougon described the first case in 1812. The most recently recorded case seems to be that of Ashton and Munro (1948). This was a Cypriot, aged 23, who, like this girl, had bilateral coronary aneurysms, and who died suddenly with no previous significant ill-health. The aneurysms were smaller than in the present case. The valves and great vessels appeared to be normal. The authors were unable to obtain any histology.

Rigdon and Vandergriff (1943) review 52 cases from the literature and include one of their own. These authors discuss the possibility of congenital anomalies in the coronary arteries—defects in the muscle coats at points of bifurcation and branching such as have been demonstrated in the cerebral arteries, and they instance the work on this of Forbus (1930).

Mycotic aneurysms may occur in the coronary arteries, due to infective embolism of the vasa vasorum, and are especially likely to occur in septicæmia with vegetations on the aortic valves. In some of the reported cases this pathology seems obvious. Stengel and Wolferth (1923) reviewing 264 cases in which mycotic aneurysms were found noted coronary aneurysms in 7.

This possibility cannot be excluded here, though the valves and endocardium appear quite

normal. The existence of healed mycotic aneurysms becomes more likely since septicæmic conditions have become amenable to treatment.

Multiple aneurysms producing a beaded appearance of the coronary arteries may occur in periarteritis nodosa. There is nothing to suggest the condition in this case. Atheroma is often described as a cause but it is extremely common at all ages while aneurysm is very rare.

(Figs. 1 and 2.) In the section of the left coronary artery the muscle coat appears to become

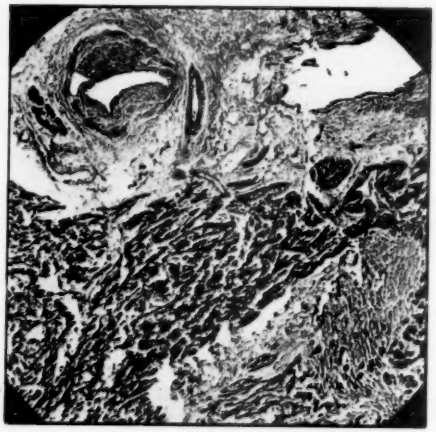

FIG. 1.

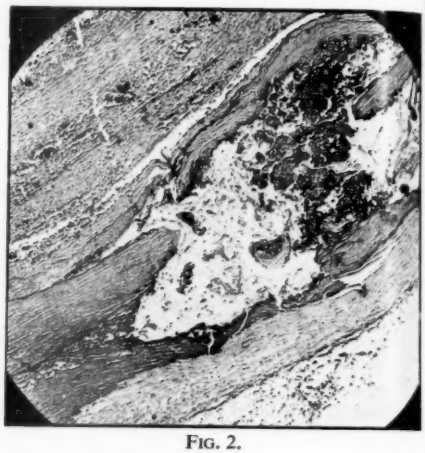

FIG. 2.

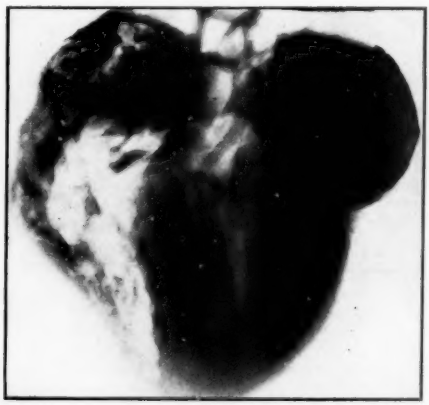

FIG. 1.—Photomicrograph of heart muscle × 32, to show interstitial fibrosis of myocardium due to obliterating process in coronary arteries which is also seen in a vessel in the photograph. (H. and E.)

FIG. 2.—Photomicrograph × 32, of wall of aneurysm of coronary artery which shows ossification. (H. and E.)

← FIG. 3.—X-ray of the specimen showing calcified aneurysms and their size in relation to the heart.

defective before the commencement of the aneurysm, though with the considerable distortion produced by the lesion this is arguable and cannot be definitely demonstrated.

(Fig. 3). Post-mortem X-ray shows the relative size of the aneurysms.

It is suggested tentatively that these aneurysms are congenital in origin and similar in pathogenesis to the more common lesions which occur in the arteries at the base of the brain and in the region of the cavernous sinus.

Acknowledgment is due to Dr. Martin Bodian in whose department at the Hospital for Sick Children, Great Ormond Street, the dissection was carried out and the sections cut. The specimen is preserved in the museum there.

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Thyrotoxicosis Treated with Thiouracil.—W. M. L. TURNER, M.D. (for C. T. POTTER, F.R.C.P.).

Jean J., born April 1945.

Admitted to hospital 2.9.50. Discharged 19.10.50.

History.—Enlarged thyroid since 18 months of age, much increased in size within past two months with loss of weight, 5 lb. Very nervous, emotional and irritable, poor appetite during past two months. About eighteen months previously she had a period when she had night terrors, insomnia, and was extremely nervous and depressed. This lasted three to four months and improved when the family moved house.

Family history.—Sister aged 9 months, well. Both parents well but nervous; some domestic tension.

On examination.—Tall thin girl, weight 50 lb. Well-marked exophthalmos, ocular movements normal, absence of wrinkling of forehead. Soft generalized swelling of thyroid, with bruit and thrill over gland; neck circumference 10½ in. Pulse 130 per minute, sleeping 110 per minute, regular. Slight coarse tremor of fingers. Slight intermittent pyrexia, 99–100° F.

Investigations.—X-ray chest and neck normal, no retrosternal goitre. X-ray skull, sella turcica normal. Wrist: bone age 6 years. Blood cholesterol 145 mg.%. Blood: W.B.C. 11,200; polys. 38, lymphos. 52, eosinos. 9, monos. 1%. Radioactive iodine excretion test (Hammersmith Hospital) 11.9.50: twenty-four hours after 10 μc. I^{131}, 0–8 hrs. 3·8%, 8–24 hrs. 1·8%, 24–48 hrs. 2·1%; total 7·7% (normal 35–70%, hyperthyroidism 4–17%). B.M.R.: First reading + 20%, others ± 1%.

Treatment.—Methyl thiouracil 25 mg. b.d. for three weeks then t.d.s. for eight weeks (as out-patient).

Progress.—Improvement in general condition with decrease in nervous symptoms, increase in weight, enlargement of gland.

13.1.51: Complaint of slight dysphagia, weight 58 lb., exophthalmos less marked. Appearance suggestive of early myxœdema, placid and rather slow of speech; neck circumference 12½ in. Methyl thiouracil reduced to 25 mg. b.d. and thyroid sicc. gr. ¼ b.d. given.

10.2.51: No change, dysphagia present, placid. Neck circ. 11¾ in. E.C.G. normal tracing.

Readmitted to hospital 20.2.51. All treatment suspended. Height 47 in., weight 52½ lb., neck circ. 11½ in. Pulse-rate 130–140 per minute. Blood cholesterol 103 mg.%. B.M.R.: − 7% to − 1%.

Comment.—This patient illustrates the value of the radioactive iodine excretion estimation as an aid to diagnosis since the basal metabolic rate is so unreliable in children. She was very sensitive to thiouracil and adjustment of dosage failed to control the thyrotoxicosis without causing excessive glandular enlargement. Surgery is contemplated but the published reports stress the danger of post-thyroidectomy hypothyroidism in these children.

Dr. Felix Brown described the psychological features of her juvenile anxiety state which was not especially characteristic of thyrotoxicosis. She improved with play therapy but was having thiouracil at the same time.

Dr. B. E. Schlesinger advised a limited partial thyroidectomy with continued thiouracil treatment should it be required afterwards.

Mr. T. Levitt stated that were this child investigated at the New End Thyroid Clinic a partial thyroidectomy would be performed.

The President also advised surgical treatment and **Dr. Alex Russell** agreed.

POSTSCRIPT.—A partial thyroidectomy has since been performed on 19.3.51 with satisfactory immediate result.

Familial Dwarfism.—BERNARD LAURANCE, M.R.C.P. (for MARY WILMERS, M.D.).

Trevor aged 8½ years, and Linda aged 5¼ years, are two dwarf siblings. Their father is 5 ft. 10 in. in height and their mother 5 ft. 4 in. The parents are unrelated and deny any dwarfism in their ancestors.

The mother has a normal living male child by her first marriage, who is now aged 20. By her second marriage she has had one miscarriage and six sibs as follows: Male (dwarf) died aged 7; male (dwarf) died aged 9 months; female (dwarf) died aged 4 years; male (dwarf) alive aged 8 (Trevor); female (dwarf) alive aged 5 (Linda); normal male alive aged 5 months. All of the first three sibs died of pneumonia.

A summary of these dwarfs' details follows:

Past history.—After normal pregnancies they were born at full term by normal deliveries.

Trevor's birth weight was 4 lb. 5 oz. and Linda's 5 lb. They were breast fed for twelve and nine months respectively and reached their developmental milestones at normal ages. Trevor had measles at the age of 6 years and Linda at 3 years.

Present state.—They are both alert and of slender physique. No testicles can be palpated in Trevor. Their measurements are as follows:

	Trevor	Linda
Height	40½ in.	37½ in.
Lower measurement	21 in.	18½ in.
Arm span	37 in.	34 in.
Head circumference	16½ in.	16 in.
Weight	25 lb.	21 lb.

Investigations.—X-ray skull: Pituitary fossa small but within normal limits. X-ray long bones n.a.d. Bone age 2–4 years (Trevor); 2–3 years (Linda). X-rays chest and abdomen n.a.d. Hb 106%. White cell counts and differentials normal. Blood sugar curves: high flat curve in Trevor; normal in Linda. Blood urea: 32 (Trevor); 29 (Linda) mg. per 100 ml. Urea clearance: 64% (Trevor), 74% (Linda) average standard clearance. W.R. negative (both). Tuberculin jelly test: positive (both). Serum calcium 9·6 (Trevor), 9·7 (Linda) mg. per 100 ml. Blood cholesterol 310 (Trevor), 286 (Linda) mg. per 100 ml. 17-ketosteroids normal (both). Tryptic activity in stools normal (both). Psychologist's report: Feeble-minded (both).

Progress.—They have been treated with tab. thyroid sicca gr. ¼ b.d. which, in the mother's opinion, has benefited them both, especially Trevor. After ten weeks' treatment, Trevor's blood cholesterol was 260 mg. per 100 ml., and after six weeks' treatment, Linda's was 270 mg. per 100 ml.

Discussion.—The deceased siblings of these two dwarfs attended other hospitals whose records confirm that they were also dwarfs.

The surviving baby brother of 5 months appears normal in every respect and the mother remarked how much he resembles his stepbrother, while all the dwarfs had a very similar facial appearance. The two dwarfs shown, besides being microcephalic, have similar, rather old-looking faces.

Only the brother, who died at 9 months, had been examined post mortem. The pituitary and thyroid glands were small, the thymus absent, and the adrenals were normal. No histological examination had been performed.

Physical characteristics.—Although apparently normally proportioned on superficial examination, Trevor's lower measurement (21 inches) is greater than his upper measurements (19½ inches) instead of the reverse, as in the normal. Linda's measurements are almost equal, a state not normally attained until the age of 10 or 11 years. Presumably, therefore, when they stop growing, they will be dwarfed, but of normal proportions.

Ætiology.—Possible causes of this dwarfism were investigated. As all the dwarf siblings had died of pneumonia, fibrocystic disease of the pancreas had to be and was excluded. Although their blood cholesterols were a little raised, they were too alert to have hypothyroidism. Evidence of other hormonal deficiencies was lacking and hence, with their clinical features, pituitary dwarfism was improbable. Primordial or genetic dwarfism appeared unlikely since these patients' mental, sexual and bone development were retarded. On account of the lack of osseous development, ovarian agenesis in the girl and the rather doubtful condition of testicular agenesis in the boy also appeared unlikely.

The most probable explanation of this dwarfism occurring in one generation is that the condition is due to a recessive gene. Statistically, only 1 in 4 siblings would be expected to be affected in such a case, but, in so small a sample, a higher incidence is possible. An incomplete dominant gene is another possibility, but less likely as none of the relatives in the two preceding generations were affected.

One is forced to the rather vague conclusion, therefore, that in these children there is a diminished capacity of the tissues for normal growth due to an hereditary genetic variation.

The President: I doubt the wisdom of giving thyroid to children like this and who are already shown to be feeble-minded.

Dr. Alex Russell: The dimensions of both children display an interesting pattern in that the lower segments (as an index of lower limb growth) are in advance for their age, whereas the span (reflecting upper limb growth) shows absolute and relative retardation. The discrepancy is as yet less advanced in the younger sib. This disproportion is not typical of a growth failure due to systemic disorder, including endocrine defects, and strongly suggests a heredo-familial or genetic trait which may or may not have been linked with dwarfism in their forebears.

Section of Ophthalmology

President—M. L. HINE, M.D., F.R.C.S.

[*December* 14, 1950]

DISCUSSION ON THE NEWER ANTIBIOTICS IN OPHTHALMOLOGY

Professor Arnold Sorsby [*Abstract*]: The concentration of antibiotics obtained in the tissues on systemic administration applies only to the vascular part of the eye: the conjunctiva, sclera, choroid, and the adnexa. The avascular part of the eye, the cornea, aqueous, and vitreous present a specific ocular problem. The blood aqueous barrier keeps back penicillin and streptomycin unless they are given in high doses systemically. The eye is, in fact, as much a double organ pharmacologically as it is optically. The recorded studies on intra-ocular levels of penicillin have shown that subconjunctival injections offer the readiest means of obtaining high intra-ocular levels. Such injections are superior to the use of drops and ointments, which give but poor results, and to systemic administration which requires very high doses and gives results that compare poorly with those obtained by subconjunctival injection. If adrenaline, or other vasoconstrictors, are added to the solvent of the penicillin, the levels obtained are not only higher but more persistent. Experimentally it is possible to control any infection of the cornea, anterior chamber or vitreous caused by penicillin-susceptible organisms, if adequate doses of penicillin are administered subconjunctivally sufficiently early. An eye with panophthalmitis is beyond treatment, and clinically it is essential to learn to recognize early signs of intra-ocular infection.

Experimentally streptomycin behaves similarly to penicillin in many respects. The white purified streptomycin at present readily available is well tolerated either as drops, ointment, or subconjunctival injection. Drops can be used in a concentration of 0·01 gramme per ml.; ointments are well tolerated up to 0·1 gramme per gramme of ointment base. Ointments are best made up by the direct incorporation of streptomycin into the ointment base without preliminary solution, and a satisfactory ointment base is 90% petroleum jelly and 10% liquid paraffin. Subconjunctival injections can be given to the limit of solubility: 0·5 gramme is soluble in 1 ml. water. The prolonged use of streptomycin, whether in ointment form, or as subconjunctival injections, presents some difficulties. With the ointment a rather irritative dermatitis of the lids tends to develop, whilst repeated subconjunctival injections also tend to produce local irritation. As with penicillin the addition of adrenaline to the solvent used for subconjunctival injection is of considerable help. The aqueous levels obtained with 0·5 gramme of streptomycin in 1 ml. water tend to be at a therapeutic level up to about twelve to sixteen hours. Considerably higher levels are, however, obtained when adrenaline is used as a solvent, and these levels persist up to at least thirty-six hours. The levels obtained by subconjunctival injection are considerably in excess of those obtained by intramuscular injection.

Experimental *Ps. pyocyaneus* infection of the cornea, which runs a disastrous course when untreated, responds very well to subconjunctival injection of 0·5 gramme streptomycin in 1 ml. adrenaline. A single injection is adequate if given within three hours of infection.

The clinical results obtained by streptomycin are discussed in some detail by Dr. Norman Bailey. The findings are essentially:

(1) Good results in cases where a streptomycin-susceptible organism can be demonstrated —as in an isolated case of tuberculous conjunctivitis and in a series of cases of infection of the cornea due to Gram-negative bacilli. (Such infections present a characteristic picture which can be recognized clinically: instead of an infected margin there is a sloughy base with much corneal infiltration; and hypopyon need not be present. The corneal reaction is essentially a rapid melting away of tissues consistent with the proteolytic action of Gram-negative bacilli.) For corneal infections by Gram-negative organism, the method of choice would be subconjunctival injection of 0·5 gramme streptomycin in 10 minims of water and 5 minims adrenaline 1 : 1,000. For tuberculous infections of the conjunctiva it is presumably better to use streptomycin systemically.

(2) Results were also good in tuberculous keratitis where the tuberculous ætiology is fairly definite.

(3) Promising results were obtained with phlyctenular ophthalmia, in which the acute attacks appeared to be cut short, and remissions made less frequent by a course of streptomycin systemically.

(4) Results were disappointing in iridocyclitis and periphlebitis of assumed tuberculous origin.

Preliminary experimental results with aureomycin and chloramphenicol suggest that intra-ocular levels from systemic administration are likely to be poor, and that better results will be obtained from subconjunctival injection. Subconjunctival injections are, however, limited by the fact that these agents are relatively insoluble, and that the preparations at present available are highly irritating. The behaviour of these two drugs, as regards absorption and excretion in the tissues, is, however, so markedly different from penicillin and streptomycin that fuller studies are essential before their use can be properly evaluated. Another difficulty with these two agents is that whilst they promise to be effective in virus lesions of the cornea, such lesions are as yet ill-understood, and cannot readily be induced experimentally. A full assessment on an experimental basis is likely to prove exceedingly difficult. Terramycin probably presents the same problems. Some clinical results with aureomycin are recorded by Dr. Ruby Joseph.

Mr. Norman L. Bailey: Streptomycin was used either systemically or locally in 48 cases at the Royal Eye Hospital and at White Oak Hospital. The cases fell into 9 clinical groups:

Tuberculous conjunctivitis.—A child with a large sloughing ulcer in the left inferior fornix, shown on biopsy to be tuberculous, was treated with intramuscular streptomycin 0·5 gramme per day for thirty days. Resolution of the lesion was rapid and uneventful, and eighteen months after treatment there was no sign of the lesion and there had been no relapse. (Demonstrated to the Meeting.)

Acute conjunctivitis due to penicillin-resistant organisms (6 cases) cleared up within forty-eight to seventy-two hours on local treatment with streptomycin by drops or ointment in concentrations between 0·05 and 0·1 gramme per ml. given at intervals varying between a half and four hours. One case was given subconjunctival injections of 0·5 gramme daily for three days.

Acute dacryocystitis due to *B. proteus* (one case) cleared quickly on systemic streptomycin after systemic penicillin had left it unimproved.

Infected corneal ulcer (9 cases) due to organisms resistant to penicillin responded well to daily subconjunctival streptomycin, the usual dose being 0·5 gramme in 1 ml. of fluid. All cases were left with a quiet eye except one case which was initially hopeless; 3 cases had a poor visual result of 3/60 or less, due to dense corneal scarring—2 of these had a severe infection and the other relapsed after treatment had been stopped.

The remaining cases did well visually, one case (Demonstrated) getting 6/9 and two 6/12 corrected vision. One case did not return after getting 6/36 with a mydriatic uncorrected, while a baby with ophthalmia neonatorum—who was treated with streptomycin by drops and intramuscularly—had a thin residual scar.

Tuberculous keratitis.—One case (Demonstrated), treated with intramuscular streptomycin 1 gramme per day for two months, improved from hand movements both eyes to 6/60 right eye and 6/9 left eye, corrected vision, as the bilateral active lesions settled down.

The other 2 cases treated were almost as satisfactory.

Eales' disease.—The effect of intramuscular streptomycin in 4 cases of Eales' disease was dubious and indefinite.

Iridocyclitis.—Six cases of chronic iridocyclitis suspected of being tuberculous on clinical grounds but with no definite evidence, were given intramuscular streptomycin 0·5 gramme per day for a month.

The result has been poor, with slight improvement in 4 of the cases.

Phlyctenular conjunctivitis.—17 cases who did not respond to the usual treatment were given systemic streptomycin, the final dosage being 10 mg. per lb. body-weight per day for two months. The effect was good, both immediately on the active lesion and remotely in greatly reducing the frequency of the relapses.

Of the 14 active cases, 5 cases were clear within ten days and all but 2 were improved within two weeks. 5 cases had no relapses at all and 9 relapsed in the first three months.

13 cases have now been followed for between fifteen and twenty-eight months and only 2 have relapsed after the first three months following the course, when relapses were frequent; 1 of these cases is now having recurrent attacks as badly as before and 1 has had one attack lasting a month.

Post-operative intra-ocular infection.—One case, due to penicillin-resistant organisms, has retained an eye in which some useful vision may be obtained after needling.

Dr. Ruby Joseph: The 4 cases shown this afternoon represent the whole of our experience at the Royal Eye Hospital with aureomycin. 3 cases received a subconjunctival injection of 10 mg. of ophthalmic aureomycin in 1·0 ml. of solvent (containing atropine 1/40 grain, cocaine 1/8 grain, and adrenaline 5 minims). The injection was well tolerated at the time

of injection, but gave considerable irritation, coming on about two hours later and persisting for several hours. Though the discomfort wore off within hours, œdema of the lids and conjunctival injection, hæmorrhages, as also some mucoid discharge persisted for several days. Two of the three patients received a second injection on the 2nd and 3rd days after the first injection respectively. There was no question of giving a third injection owing to the irritative reactions.

As for the results, they may be described in these terms:

(1) *Disciform keratitis.*—In this patient the response was good; the opacity was clearing visibly day by day. Now, four weeks after the first injection, there is little left except a fairly dense central opacity.

(2) *Two cases of dendritic ulcer.*—Both these cases gave a far less definite response. Staining disappeared within five days in one patient, and after two days in the second patient. In both cases the subepithelial track of the dendritic ulcer appeared to be uninfluenced. The older of these 2 cases showed a mild relapse with a dendritic ulcer a fortnight after injection. Whether either of them was influenced favourably is an open question.

Apart from these 3 cases treated with ophthalmic aureomycin, there is 1 patient with epidemic keratoconjunctivitis, first seen two days ago. By then we had available almost pure aureomycin. She was given 10 mg. in 1 ml. of solvent two days ago. The injection was well tolerated and there were no subjective after-effects. The lids, however, were swollen twenty-four hours later, and there was a fair amount of chemosis. Today the condition is substantially the same. (Demonstrated.)

It would be presumptious to draw any definite conclusions from this very limited experience. The suggestion does, however, emerge that aureomycin may prove a valuable agent in disciform keratitis, and, if suitable methods of administration become feasible, perhaps also in dendritic ulcer.

Dr. D. Ainslie: *Clinical studies with aureomycin.*—About eighteen months ago, when aureomycin first became available in England in reasonable quantity, it was decided to investigate its clinical properties in relation to ophthalmology. I have been fortunate in having the opportunity of examining and treating the cases so kindly referred to the Institute of Ophthalmology by surgeons of the Moorfields, Westminster and Central Eye Hospital.

Aureomycin had been tried out in the field of general medicine, both experimentally and clinically, for some time previously and it had been found to be of value against all types of coccal organism and a number of Gram-negative bacilli. Of even greater interest, however, was its reported value in dealing with a number of virus infections, rickettsial diseases, psittacosis, lymphogranuloma inguinale and primary atypical pneumonia. Accordingly it was decided to treat ophthalmological cases of infection which had failed to respond to other treatment, cases in which the causative organism was known to be insensitive to penicillin or sulphonamides and, in particular, diseases believed to be due to viruses.

So far as methods of administration go, systemic administration has been by mouth in doses of 500–750 mg. six-hourly. I have not noted any serious toxic effects. One patient developed transient vertigo and headache. Most patients have suffered a little nausea and looseness of the bowels but some have not even noticed this.

For local administration, 0·5% aureomycin drops have proved useful for superficial infections and have given rise to no toxic effects whatever, even when given at minute intervals for an hour or more. Hourly administration for days causes no trouble. There have been reports that corneal excoriation may follow too frequent instillation, but I have not seen this occur.

The most generally useful method of topical application, particularly for outpatients, is ointment. The 5 mg.% ointment in a Eucerine base, which I used to begin with, caused a few mild allergic responses, but with the new commercial 1 mg.% ointment in wool fat and petrolatum I have had no trouble. The ointment appears to have a high antibiotic activity and latterly I have been using it more and more, in many cases in place of drops, as it is so much more convenient.

Subconjunctival injection is a feasible method of administration but so far I only have experience of injections in amounts up to 1 c.c. of 0·5% solution, i.e. 5 mg. of aureomycin. Apart from the pain of administration, which is much reduced by local anæsthetic, there has been no serious local reaction to this admittedly low concentration. One patient received six successive daily injections without damage.

2 cases of intra-ocular inflammation following operation have in fact been treated by subconjunctival injection. One infection was due to penicillin-insensitive *Staph. aureus* and the other to *B. coli*. The infections subsided following the treatment but the eyes were already considerably disorganized.

Subconjunctival injections will be discussed again in connexion with disciform keratitis.

We first treated with aureomycin a series of cases of uveitis. This disease was chosen because it is so frequently unresponsive to every treatment and also because of the possible virus ætiology in some instances. In addition, there had already been a few reports from America suggesting that aureomycin might be of value. In this series, however, aureomycin was not successful.

The cases treated were of the chronic or recurrent type and were characterized by fine K.P. and, in many cases, visible cells circulating in the anterior chamber. 18 such cases have been treated and, in addition, 3 cases of recurrent hypopyon uveitis and one more in which the hypopyon uveitis was part of Behcet's syndrome. All were given oral aureomycin in doses of 500–750 mg. six-hourly over one to two weeks, in addition to local treatment. The chronic cases did not improve.

Temporary improvement, such as might be accounted for by natural remission, occurred in the cases of recurrent hypopyon uveitis but no permanent cures resulted. If indeed these cases are of virus ætiology it would therefore seem that the virus is either insensitive to aureomycin or is not reached by the antibiotic. Certainly the penetration of aureomycin into the intra-ocular fluid, when given systemically or by topical application, is very slight.

In addition to the foregoing 22 cases of uveitis, 2 cases of active sympathetic ophthalmia have failed to benefit.

However, while treatment of these cases of iridocyclitis was giving negative results, the effects of aureomycin on other diseases of more certain virus ætiology were being more promising.

Trachoma.—This is almost certainly due to a virus similar to that causing psittacosis and so one would expect it to benefit. This is in fact the case. I have not been able to obtain any examples of acute stage one or early stage two trachoma, but I have treated 7 patients suffering from stage two passing into early stage three, in which cicatrization had commenced but in which there was highly active pannus—numerous sago-grain follicles and papillary hypertrophy. Further, in 3 cases it was possible to demonstrate inclusion bodies in scrapings taken from the epithelium.

All the cases responded remarkably well to aureomycin administration. All had drops and ointment locally and 3 had systemic administration as well. There was rapid clearing of the corneal ulceration, reduction in the pannus and disappearance of the papillary hypertrophy and the follicles. In 2 cases a few follicles remained but they have not altered in three months since treatment. A little vascularized pannus remains in all cases but it appears inactive. The subjective and objective improvement have been maintained in the cases over periods ranging from three to nine months after cessation of treatment.

One other case which certainly had the typical appearance of trachoma, but was peculiar in that it was unilateral and giving rise to no symptoms, and was discovered by accident, showed little or no change after a course of aureomycin. The condition remains the same today, almost a year later, and the patient is still symptom-free.

A further 5 cases of chronic trachoma have been treated with local aureomycin, with reduction in hyperæmia and considerable subjective relief. The improvement has rather surprisingly continued, even after the cessation of treatment, whereas previous treatments with Albucid, penicillin, &c., had produced very transient benefit.

These findings in trachoma certainly concur well with those reported elsewhere in the world. For instance in Uganda, Boase, who has had the opportunity of treating acute cases, has had remarkable success.

The closely allied condition of follicular conjunctivitis, due to a similar though less formidable virus, is also responsive to aureomycin. 11 cases of acute and subacute follicular conjunctivitis have been treated.

It has been said that this is a self-limiting disease, but in these cases the disease had been present for from four to seven weeks without improvement despite numerous treatments. In 2 cases there was already superficial corneal vascularization near the limbus, not in the form of trachomatous pannus but in a ring all round the cornea. In one a severe corneal ulcer had developed.

In every case improvement with aureomycin was rapid and there has been no relapse. In the first two cases I treated I gave systemic aureomycin in addition to the drops and ointment but, in view of the excellent results in the other cases with local administration alone, I doubt if this is usually necessary. In 3 cases inclusion bodies were found before treatment but none afterwards.

Two additional cases of chronic conjunctivitis, with numerous small follicles and corneal vascularization, responded well to aureomycin therapy although the condition had been present for years. However, there has been a tendency towards relapse.

3 cases of chronic keratoconjunctivitis, but without follicles, contracted abroad several years previously, were treated but with only temporary success. These looked like examples

of epidemic keratoconjunctivitis which had become chronic. American reports suggest that epidemic keratoconjunctivitis can be cured readily by aureomycin, but only if it is given in the early stages.

The common condition of mucopurulent conjunctivitis in infants usually responds rapidly to Albucid, penicillin or other remedies. Cultures from cases reveal from time to time a variety of pyogenic organisms, but not infrequently no organism can be cultured although there is obvious infection present.

I have seen within the last few months 8 cases of bilateral mucopurulent conjunctivitis in infants and young children which failed completely to respond to the usual measures including, in 5 cases, intensive courses of penicillin. In all cases culture was sterile or only a few colonies of *Staph. albus* were grown. In every case twelve hours of local aureomycin treatment produced remarkable improvement and within three to four days the condition had cleared completely, and remained cleared.

It is possible that these are examples of virus conjunctivitis, though examination of 3 of the cases has not revealed any inclusion bodies. In any case, whatever the cause, I feel that the rapid 100% results in even so short a series make it well worth while bearing aureomycin in mind when dealing with infantile conjunctivitis.

One adult with mucopurulent conjunctivitis, cultures from whom grew nothing but a few colonies of *Staph. albus*, cleared in two days with aureomycin after penicillin had failed.

There are a number of virus diseases, however, which have not responded well to aureomycin. Herpes simplex is an example. Although 2 cases with secondary infection responded readily, 12 cases of simple acute dendritic ulcer failed completely to respond. This is in contradiction with other reports, particularly from America, where a high cure rate is claimed.

In superficial punctate keratitis temporary subjective relief was the only benefit in all of the 10 cases treated.

If systemic aureomycin is given to herpes zoster ophthalmicus in the early stages the secondary lesions appear to clear more rapidly, but I have not found that it has any beneficial effect against the iridocyclitis.

4 cases of disciform keratitis have been treated. The 2 first I treated with only topical application but there was no favourable response. The 2 latter received subconjunctival injection and improved rapidly. The corneal infiltration started to improve almost at once and continued after the cessation of injections, until the eye became entirely quiet. I hope to be able to treat further cases as the initial results are certainly encouraging.

With regard to the effects of aureomycin in the treatment of infections with simple pyogenic organisms I do not wish to say a great deal, important though these applications may be. For the action is similar to that of penicillin, though aureomycin is effective over a wider range of organisms. Many strains of *Staph. aureus*, for instance, are insensitive to penicillin but respond readily to aureomycin.

I have treated 18 cases of blepharitis due to *Staph. aureus* which were insensitive to penicillin and sulphonamides when tested *in vitro*, and had indeed failed to respond to treatment with these drugs. Out of these 18 cases 10 have cleared up, and remain clear after over six months. 5 cleared up but have required further treatment owing to recurrences. 3 more have responded scarcely at all.

These results are approximately what one might, I think, expect, as the difficulty of completely eradicating the deep-seated organisms applies equally to aureomycin as to any other antibiotic, and a certain percentage of recurrences are inevitable. I would note, however, that 1 case now apparently cured had had the blepharitis for twenty-six years with only very temporary periods of relief, and 3 other successful cases had had the disease for six to ten years.

2 cases of blepharoconjunctivitis due to *Friedländer bacillus* cleared up readily after aureomycin treatment.

In addition a number of cases of conjunctivitis from whom cultures revealed non-penicillin-sensitive *Staph. aureus* have been successfully treated.

Thus it would seem that the outstanding value of aureomycin is in attacking a group of the large viruses but its power against the large army of non-penicillin-sensitive staphylococci and other cocci may, in the end, be its most useful application.

Systemic administration appears to be useless in infections of the globe itself but if higher concentrations of subconjunctival injections can be used (if a less irritating preparation becomes available), there seems to be hope in this direction.

I should like to conclude by thanking Sir Stewart Duke-Elder for his interest and encouragement and Dr. N. Ashton for examining so many cultures and smears, and the resident staff of Moorfields, Westminster, and Central Eye Hospital, for their co-operation in dealing with in-patients.

[*February* 8, 1951]

DISCUSSION ON DIABETIC RETINOPATHY

Dr. R. D. Lawrence: I intend first to outline the various disturbances of diabetic metabolism and then to consider how these disturbances might produce such a condition of, say, primary degeneration with fatty changes or some sort of degenerative change in the venous capillaries of the eye.

Diabetes is primarily a disturbance of carbohydrate metabolism in which the body cannot use carbohydrate food. An excessively high blood sugar is the first characteristic feature of diabetes, and we say that this is due to a defect of the islets of Langerhans in the pancreas making them unable to deal with the absorbed carbohydrate food. Hyperglycæmia is brought about, the sugar passing through the kidney, taking an excess of water with it, causing wastage of food, and illness and weakness on the part of the patient.

There is an important secondary mechanism. When the body cannot use enough carbohydrate to keep its metabolism going—and we find the same thing in ordinary starvation—the body starts to use fat, and the fat produces the acetone or ketone bodies which are the real danger in diabetes, and occasionally lead ultimately, without insulin treatment, to diabetic coma.

I should like to pass in review some of the many factors in this metabolic disturbance which have been blamed for the degeneration in the blood vessels of the eye. Ketone poisoning has been blamed, but I think this has been thoroughly disproved. In the type of severe diabetes with ketosis the blood cholesterol is apt to be high, and a German worker a long time ago showed that if cholesterol is injected in rabbits arterial sclerosis and atheroma are produced. But I think that explanation also can be ruled out and most of my retinal cases have normal cholesterol values. Acidosis and deficiency of calcium can also be disregarded.

A recent publication accuses the diabetic of having too low a serum protein, an increased amount of globulin disturbing that ratio. This is a matter which needs a good deal more research and, at present, I do not myself believe that such is the case, finding in my diabetic patients no disturbance of blood proteins.

I have ruled out a number of things which have been accused of causing this vascular degeneration. I should, perhaps, explain that there are two types of diabetes. We have, on the one hand, the fat middle-aged person who tends to get arteriosclerosis as years go on, and who I used to think, in the nineteen-thirties, was the only type which showed these diabetic retinopathies. But there is another type of diabetes in younger people under forty, with acetone poisoning, who formerly died very quickly without insulin. For a long time it was thought that these people did not get retinopathy, but now that they are living longer by the grace of insulin we find a large number of them—said to be 100% by some Americans—who live for twenty-five years and all have retinopathy. I do not agree with that finding. I myself have had diabetes for thirty-one years, and not long ago I had my eyes examined by Mr. Whittington and was assured by him that I had no retinal hæmorrhage. I have many patients with diabetes of a duration of over twenty-five years who also have no retinal hæmorrhage. But the affliction is all too common.

On the whole it is not the severity of the diabetes or the particular type which may produce the trouble. It is seen in both types, and in my opinion the one certain thing about diabetic retinopathy is that it is the *duration* of the disease which is the producing factor. Neither does it depend on the occurrence of general arteriosclerosis: There is a lesion typical of diabetes without arterial sclerosis and with normal blood pressure (110/70 or 140/85).

I have done nothing, therefore, to contribute to ætiology except to suggest that in some mysterious way a prolonged raised blood sugar contributes eventually to the retinal disturbance. But although we may not be able to explain the mechanism we have certain possibilities of control, even if we cannot make the people physiologically normal.

It is now thought that diabetes may not depend primarily on the islets of Langerhans of the pancreas going wrong, and that there may be another endocrine—a pituitary—factor which is concerned. It has been postulated that it is not diabetes *per se* but another endocrine pituitary factor in the background which produces these vascular changes. But recently diabetic retinopathy has been reported in hæmochromatosis and in relapsing pancreatitis where the cause of the disease is direct destruction of the islets of Langerhans with no other endocrine factor. Therefore, in my opinion, it is the factor mysterious in action of prolonged high blood sugar which produces this lesion.

My detailed knowledge of ophthalmology is not very great. I was never taught in it as a student, and never saw the back of the eye with the mechanisms with which I was then provided. But for the last twenty years I have been looking at the eyes of diabetics, sometimes twenty a day, seldom less than five, and there are a few things I would like to mention from my own observation.

Retinopathy definitely occurs without any general arteriosclerosis shown either by albuminuria or raising of blood pressure. How soon can it happen? Not usually for ten or twenty years. The earliest I have seen to occur in diabetes is after four years. It is often extremely difficult to know with a mild type of diabetic how long he has had it. You may be told that perhaps for seven years before he went to an ophthalmologist he has had mysterious white (sugar) spots on his trousers. There are many who have the disease in a mild type, not sufficient to affect their health, for very many years. But in truly severe cases there is little doubt as to when it started, and, as I have said, the earliest retinal changes I have seen were after four years.

Often these patients do not reach the ophthalmologist until the disease is rather serious, and it may be felt that there is nothing to be done about the retinopathy. In our routine examinations of diabetics we see cases in which there is punctate hæmorrhage, or aneurysm as it is now called, off and on for years. The appearance comes and goes; nothing at all may be seen for perhaps another few years and then there is a recurrence. The progress of this disease is far less rapid and severe than most ophthalmologists think. I have seen a whole shower of hæmorrhages disappear nine months after the first observation, and nothing is to be seen for five years, and then a few come back, and a few come and go for many years. I have seen a most interesting old woman, now 82, who had quite considerable disturbance of vision with heavy cholesterol nuggets at periods over fifteen years. Occasionally one may now see a punctate hæmorrhage, but there is nothing else left. Therefore the prognosis is not quite so bad as ophthalmologists think.

What does this progress depend upon? Does the control of the diabetes prevent these developments, or remove them? Most people would say "No". I am not so sure. The earliest bad retinopathies I have seen in diabetic children are in those who eat everything, take their insulin reasonably well, but always have high blood sugars. When they grow up and take their treatment more carefully in hand the initial lesion sometimes disappears and the retina becomes nearly normal.

There are, I think, two types of this process. There is one in which the veins look fairly good, even normal, but apart from that there are these hæmorrhages and the development of white spots. But there is another type in which the veins become dilated; sometimes they have a "sausage" appearance, but the arteries still look fairly good. In these cases huge pre-retinal blood vessels develop, which burst, and cause vitreous hæmorrhages. Many of them quickly develop. These retinitis proliferans cases have been just as well controlled as the others. Is it due to inborn good blood vessels, to a good heredity that so many escape this type of disease? Many of these long-standing diabetics of fifteen or twenty years' duration not only have retinal changes but other vascular degeneration. They seem to get a similar lesion in the glomeruli of the kidney. They develop an albuminuria; their blood pressure goes up, and they get "diabetic glomerulo-sclerosis". When this is added to the idiopathic retinitis the picture changes at once and ultimately comes to a renal stage with quite different types of hæmorrhage with blurring of the disc and œdema.

No doubt the condition, which I have dealt with only in general outline, will be more adequately described by later speakers. I have not touched on the physical factors, such as the necessarily high pressure in the venous ocular system, which must contribute to the fact that diabetic vascular degenerations are first and most obviously produced in the fundus.

Dr. G. I. Scott: *Diabetic retinopathy.*—Although changes in the larger veins were described by Nettleship, in 1888, it was not until 1937 that stasis in the veins was first suggested, by Mylius, as the essential factor in the causation of retinopathy in diabetes.

The significance of the venous changes was not, however, truly appreciated until our thoughts were directed away from factors such as hypertension and arteriosclerosis.

In 1943, Ballantyne and Löwenstein, reporting on a large series of diabetic patients, found that 50 per cent of those with retinal changes had normal blood pressure and that many cases showed no arteriosclerotic changes in the retinal vessels. They therefore concluded that diabetic and hypertensive retinopathy should be regarded as quite separate entities.

It is also significant that Wagener who, in 1921, thought that the retinopathy of diabetics was essentially that of arteriosclerosis wrote, in 1945, that, as a result of twenty-five years further clinical experience, he was quite definitely of the opinion that neither arteriosclerosis nor hypertension produced retinopathy of the type characteristic of diabetes.

In 1943 Ballantyne also drew attention to the capillary micro-aneurysms with which we

are all now familiar, and, in conjunction with Löwenstein, he demonstrated localized fatty degeneration in the walls of the small venules. The more recent work of Ashton has confirmed that these lesions are in fact micro-aneurysms and not merely capillary dilatations.

The above observations constitute an important advance in our knowledge, since they have directed our thoughts away from factors now recognized to be of no ætiological significance, even although it must be confessed that we are still ignorant of the cause of the venous changes.

Another noticeable feature in the literature regarding diabetic retinopathy is the marked diversity in the published figures of its incidence.

There are certainly two factors which might account for such variation. In the first place there seems to be no doubt that the incidence depends very much upon the duration for which a patient has had diabetes. In 1945, Wagener reviewed the ophthalmic findings in 1,021 diabetics, examined at the Mayo Clinic during the year 1944, in whom retinopathy of the type characteristic of diabetes was present in 29·6%. When, however, the incidence was correlated with the duration of the diabetes, it was found to be only 10·7% in those who had had diabetes for less than one year, but to be 73% in patients who had had diabetes for longer than twenty years.

It is moreover well known, as has been shown by both Joslin (1946) and Stocks (1944) that diabetics are now living longer. Joslin and his associates at Boston have studied this question in conjunction with the Statistical Department of the Metropolitan Life Insurance Company of New York, in a series of 28,000 diabetics treated at Boston since 1898. Their figures show, for example, that immediately prior to the introduction of insulin in 1922, a child getting diabetes at the age of 10 years had an expectation of life of only 2·6 years, whereas the expectation of life in 1938 would have been 39·8 years: a young adult getting diabetes at 30 years of age, in say 1920, had an expectation of life of only 6·3 years, whereas by 1938 it had increased to 27·6 years.

When these findings are linked with the observations made by Wagener, regarding the marked rise in the incidence of retinopathy the longer the duration of the diabetes, it is at once apparent that the observation of earlier writers, that retinopathy rarely occurred in young diabetics was, at that time, perfectly correct, for, in pre-insulin days, the young diabetic rarely lived long enough to develop it.

During the past few years I have, in conjunction with Dr. Halliday Croom, examined 150 diabetics, all of whom have had the disease for periods varying from fifteen to twenty-six years. A preliminary report on the first 60 cases was published by us in 1949, but I would like, if I may, to give you a short report of our findings in this larger group of cases:

Ophthalmological findings.—Changes typical of diabetic retinopathy were present in 62 (41·3%) of our patients, a rather larger percentage than was recorded in our previous report. Micro-aneurysms were seen in 34 patients, and were the only sign of retinopathy in 5 of the cases.

Micro-aneurysms were most numerous temporal to the disc, but, in about a quarter of the cases, isolated aneurysms were also seen in the nasal half of the retina.

The hæmorrhages were mainly deeply situated, small and roughly round in shape, although a few were superficial and "streaky". In some cases the larger, round hæmorrhages presented the typical appearance which Hanum (1938) has described as being like the impression which might be made by a minute sponge. A few cases showed larger "blot" hæmorrhages which were sometimes almost subhyaloid in appearance. Typical hæmorrhages were seen in 53 of the 62 cases of retinopathy.

The exudates were white and well-defined, and in the early stages resembled flecks of icing-sugar or powdered snow. Only in the arteriosclerotic patient, or in the more advanced cases, did we see the hard, so-called soapy, yellowish-white or white plaques of exudate described in most textbooks. Exudates were present in 47 of the 62 cases with retinopathy.

Six patients with retinopathy developed severe hæmorrhage into the vitreous, with subsequent development of retinitis proliferans. Two of these patients had been under our observation for some years previous to the present investigation, when only minimal retinal changes were present, and the subsequent course of events showed points of interest. In both cases the signs of retinopathy were slight. The first patient then developed a single, not very large, preretinal hæmorrhage, followed shortly afterwards by a sudden hæmorrhage into the vitreous; the second patient also showed minimal changes and yet suddenly bled into the vitreous. These two cases seem to demonstrate quite clearly that bleeding into the vitreous is not an advanced stage of retinopathy, requiring gross lesions in the veins, or an advanced degree of retinopathy, as a necessary precursor. Hanum noted the same occurrence in one of the cases which he recorded in 1938, and, as he aptly expressed it, "from these preretinal hæmorrhages there seems to be but a floating transition to the apoplectiform hæmorrhages, which involve the vitreous, and, probably always, give rise to proliferative processes".

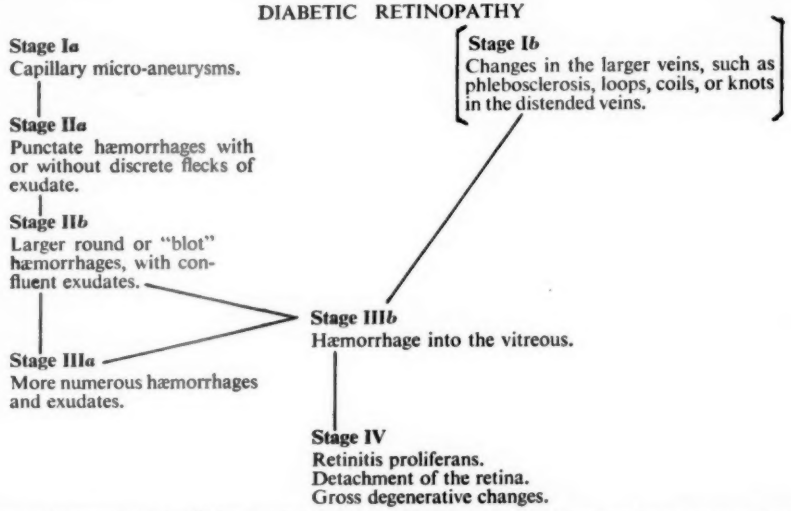
Engorgement of the veins, although evident in most of the cases of retinopathy, was not always a marked feature, and, if attention had not been drawn to the presence of pathological changes such as micro-aneurysms, hæmorrhages or exudates, the congestion of the veins might well, in many cases, have been classified as within physiological limits. Congestion of the veins only reached a marked degree in 10 of the 62 cases with retinopathy.

Arteriosclerotic changes in the vessels were minimal or absent, except in seven patients, four of whom were hypertensive. Of the 62 patients with retinopathy 43 showed normal retinal arteries.

As Ballantyne has emphasized, the changes which we sometimes see in the larger veins do not represent an advanced stage of diabetic retinopathy, and they can occur in the absence of the hæmorrhages which we regard as characteristic. Moreover, such changes in the veins are not specifically diabetic since they may occur in cases of hypertensive retinopathy, as well as in other conditions.

Philps (1946), for example, recorded their occurrence in a non-diabetic patient who, for many years, had had fibrosis of the lungs with raised venous pressure.

In the present state of our knowledge I think that it might be useful to us, as clinicians, to adopt a classification, slightly different from that used by the pathologist, to illustrate the various stages in the clinical course of the disease (Fig. 1).


DIABETIC RETINOPATHY
Stage Ia
Capillary micro-aneurysms.
Stage Ib
Changes in the larger veins, such as phlebosclerosis, loops, coils, or knots in the distended veins.
Stage IIa
Punctate hæmorrhages with or without discrete flecks of exudate.
Stage IIb
Larger round or "blot" hæmorrhages, with confluent exudates.
Stage IIIb
Hæmorrhage into the vitreous.
Stage IIIa
More numerous hæmorrhages and exudates.
Stage IV
Retinitis proliferans.
Detachment of the retina.
Gross degenerative changes.

NOTE.—As regards "mixed" forms of retinopathy, changes typical of hypertensive or arteriosclerotic retinopathy may, of course, be seen in association with Stages I*a* or *b*, II*a* or *b* or III*a* of diabetic retinopathy.

FIG. 1.—Classification—to illustrate the various stages in the clinical course of diabetic retinopathy.

At the commencement, the process is, as it were, confined within the walls of the veins, with engorgement of the veins and the development of multiple micro-aneurysms, or, in a smaller group of cases with characteristic, but not specific, changes in the larger veins. (Stages I*a* and I*b*.)

The next stage is the escape of blood into the deeper layers of the retina, with or without the formation of exudates, the earliest stage consisting of punctate hæmorrhages with perhaps a few flecks of exudate. (Stage II*a*.) As this process progresses the condition gradually changes to the stage of dot and blot hæmorrhages, with more confluent exudates. (Stage II*b*.)

Even in patients with diabetes of long duration, as in our series, the retinal changes fall into Stages I*a*, II*a* or II*b*, in over 75% of cases.

In the minority, in which further deterioration occurs, the progress of the disease follows one of two very different courses. A certain proportion show an exacerbation of the changes seen in Stage II*b*, i.e. the hæmorrhages become more numerous and the exudates more confluent and more waxy in appearance. (Stage III*a*.)

In an appreciable number, however (9·7% in our series), Stage II*b* may suddenly be followed by hæmorrhage into the vitreous and by subsequent proliferative changes.

It is also to be noted that hæmorrhage into the vitreous may follow immediately upon Stage I*b* without any intermediate phase of hæmorrhages and exudates.

Clinical examination.—From the general point of view, 34 of the 150 cases which we examined were found to be free from clinical evidence of degenerative disease. In 2 of these cases the onset occurred over twenty-six years ago.

In this series it would appear, therefore, that degenerative lesions are not inevitable even as late as twenty-six years from the onset of the disease.

In 68 of our patients the systolic blood pressure was below 140 and the diastolic pressure was below 90; these were classified as normal. In another 68 cases the systolic pressure was 160 or more, or the diastolic was 100 or more, and these were classified as hypertensive. The remaining 14 exhibited blood pressures between these two levels, and were regarded as doubtfully hypertensive.

The distribution of the hypertensive cases is shown in Fig. 2. It will be noted that a considerable number (35 out of 62) of these cases with retinopathy showed no evidence of hypertension.

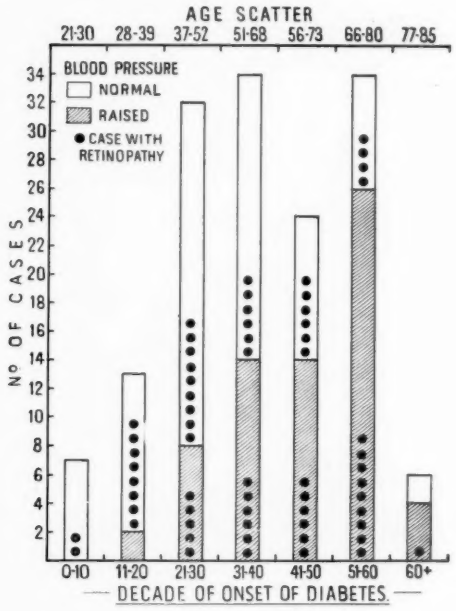


FIG. 2.—Age scatter of cases with retinopathy. To illustrate that hypertension is not a necessary factor in the production of retinopathy in diabetics.

In addition, it was noted that although over a third of our patients showed clinical evidence of peripheral arteriosclerosis, nearly two-thirds of our cases with retinopathy had no clinical evidence of general arteriosclerosis.

Two cases only showed albuminuria and œdema, suggesting that the nephrotic syndrome associated with diabetes, while a pathological entity is indeed a clinical rarity as was, in fact, suggested by Kimmelstiel and Wilson in their original description of the condition.

A careful analysis of the case records was made in an attempt to assess the relationship between the severity or control of the diabetic state and the development of degenerative changes.

The severity of the diabetes was assessed by the dosage of insulin required, and the control of the condition by the general well-being of the patient, the degree of glycosuria, and the frequency of reactions.

In this series, as in our previous review, there was no significant correlation between the severity of the diabetes and the development of cardiovascular or retinal complications.

As regards the control of the diabetes, we reported in the review of our first 60 cases that we found no evidence of any correlation between the occurrence of vascular or retinal changes and the control of the diabetic state. A study of our present larger series of 150 patients seems to suggest, however, that control of the diabetic state may, in fact, be an important factor in lessening the incidence of degenerative changes.

When we divided our 62 cases with retinopathy into those whom we knew were poorly controlled and those who appeared to be controlled on every occasion upon which they were examined, there were 30 in the first group and 32 in the second. We had, however, a large number of patients (51% of the 150) whom we labelled "defaulters", as they were not regular in their attendance at the follow-up clinic. The defaulters were almost equally divided between our "uncontrolled" patients and those apparently well controlled upon the occasions on which they did attend.

With regard to the incidence of retinopathy, however, we found that 45 (72%) of the 62 patients with retinopathy were defaulters, whereas there were only 6 defaulters among the 34 patients who were free from all signs of degenerative disease (Table I). It is certainly

TABLE I.—TO SHOW HIGH PERCENTAGE OF "DEFAULTERS" AMONG PATIENTS WITH RETINOPATHY

REVIEW OF PATIENTS WITH DIABETES. 150 CASES

	"Defaulters"	
	Number	Percentage
Cases with retinopathy (62)	45	72·0
Cases with degenerative disease of one kind or another (116) ..	71	61·0
Cases free of degenerative disease (34)	6	18·0

a factor of great practical importance and worthy of further study in a larger group of cases.

If it is true that really strict control of the diabetic state will lessen the incidence of degenerative changes, then it is obvious that we would be justified in using every effort to try and convince our patients of the absolute necessity of adequate control and supervision of their diabetic state.

We do not know why the retinal changes take place, and we do not know how to treat the retinopathy when it does occur. It would seem, however, that we may, at least, hope to prevent what we cannot cure.

In conclusion, I should like to express my indebtedness to Dr. J. Halliday Croom, with whom I made the study of the 150 patients to whom I have referred.

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Dr. Norman Ashton (*Institute of Ophthalmology*): A great deal of work has been done in the past in the study of the pathological changes in the diabetic retina and the characteristic lesion of this retinopathy, namely the capillary micro-aneurysm, was first clearly described by MacKenzie and Nettleship in 1879. The discovery did not, however, give rise to great comment and no further interest appears to have been taken in the lesions until 1943 when they were rediscovered and studied in greater detail by Ballantyne and Löwenstein. Their careful work stimulated great interest and a considerable amount of research work, based upon their original observations, is now in progress both here and in America.

At the Institute of Ophthalmology we have now examined post-mortem material, including the eyes, from 121 diabetic subjects; in 110 of which the data are sufficiently complete to analyse. 71% of the cases were females; retinopathy in various stages was present in 68% and Kimmelstiel-Wilson's disease was seen in 36%. Our findings in this series will be more fully dealt with in a subsequent paper.

A diabetic retina mounted in a glass sphere clearly shows the two types of hæmorrhages which may be seen ophthalmoscopically: the irregular so-called "blot" hæmorrhages and the round, well-defined "dot" or punctate hæmorrhages which Ballantyne and Löwenstein found, in flat preparations of the retina, to be capillary micro-aneurysms. In 1948 Friedenwald improved upon their original techniques by applying the McManus periodic acid (Schiff) stain to the flat retina; the vessels stain an intense red and a more deeply staining basement membrane may be seen in the subendothelial layer. These staining properties are presumably due to the presence of a muco-polysaccharide protein complex within the basement membrane. The technique applied to the diabetic retina clearly demonstrates the micro-aneurysms; they are seen to be remarkably localized, often extremely thick walled and the adjacent vessel may appear normal. These appearances were puzzling at first, because it was difficult to see how an aneurysm could reach such a size without distortion of the surrounding vessel; we had, however, noted an indentation in the vessel wall opposite the aneurysm and the explanation for these appearances is now clear—as I shall explain later. They may become completely obliterated and so form the white dots seen ophthalmoscopically.

We have shown (Ashton, 1949) that the lesions are usually 20–30 microns in diameter, that is at the limit of ophthalmoscopical visibility; larger ones of 75–100 microns not infrequently occur. Serial sections through one of these lesions proved beyond doubt their aneurysmal nature. Further sections indicated the importance of the basement membrane in the pathological process; sometimes it is greatly thickened and in other instances it appears to split and disintegrate at the edge of the aneurysm. Some of these lesions commence as minute diverticulæ arising on one side of the vessel wall and from this stage they gradually enlarge, their walls becoming thickened by a translucent hyaline material. However, they appear to arise more frequently from loops in the vessels which become varicose, exudate oozes through the vessel walls and the two loops become adherent—it is this formation which explains the development of a large aneurysm on an otherwise normal-looking capillary (Fig. 1).

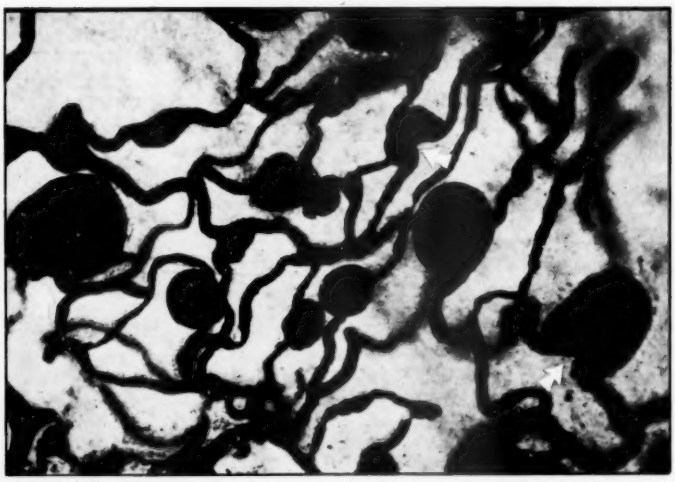

FIG. 1.—Injected diabetic retina showing many micro-aneurysms, beading, looping and irregularity of the capillaries. The arrows indicate those aneurysms which can be seen to arise from varicose loops. (× 266.)

We have now improved upon this staining technique by injecting the central retinal vessels with Indian ink by means of a fine glass cannula, an electric pump and a dissecting microscope (Ashton, 1950*a*). By this means all the vascular irregularities in the retina are well shown and in advanced cases they are very gross indeed (Fig. 1). In some retinæ the artery was injected with a red dye and the vein with black, demonstrating, as Ballantyne had stated, that the lesions are largely confined to the venous side. Similarly neoprene injections of the vessels may also be made and the method has the advantage of preserving the normal contours (Fig. 2). These preparations show particularly well the development of aneurysms from varicose loops.

As Ballantyne has pointed out the vessels in diabetic retinopathy undergo fatty degeneration and this is most marked in the region of the aneurysms. At this site also the permeability of the vessel wall is increased and red cells pass through it, forming the "blot" type hæmorrhage: thus also albuminous exudates, together with the fatty globules, exude through the vessel wall and so form the typical waxy exudates in the outer molecular layer.

The question naturally arises as to whether micro-aneurysms may exist outside the retina in cases with diabetic retinopathy. It is extremely difficult to decide from tissue sections, even serial sections, whether such lesions exist or not. We have, therefore, in some 30 diabetic patients, with and without retinopathy, examined flat preparations of the serous membranes of the pleura, meninges, renal and liver capsules, in order to obtain a picture comparable to the retina; and the brain, liver, kidney, and lung were examined by injection techniques followed by the clearing of thick slices with xylol; in this way the tissue could be studied in depth. All the other vessels of the eye have also been examined, and we have recently injected a diabetic gangrenous leg with Indian ink and examined the whole capillary network in a series of slices, but have not succeeded in finding any aneurysms outside the retina except in the glomerulus. This is contrary to the experience of McCulloch and Pashby (1950) who examined the conjunctival vessels in diabetic and non-diabetic patients; they found aneurysms more frequently among diabetics than in normal individuals and more commonly in diabetics with retinopathy than in those without. On the other hand, Friedenwald (1950) found only one conjunctival aneurysm in 60 successive cases of diabetic retinopathy. Further work is, therefore, necessary to elucidate this point but it is felt that the conjunctival tissue, being exposed and subject to recurrent minor trauma, is not a suitable site for the study of extra-ocular capillaries.

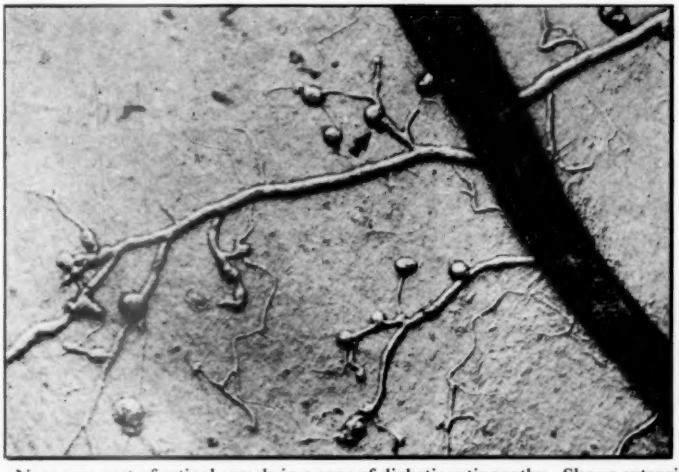

FIG. 2.—Neoprene cast of retinal vessels in a case of diabetic retinopathy. Shows extensive micro-aneurysm formation associated with beading. The arrow indicates the origin from a varicose loop. (× 93.)

Friedenwald (1950) has studied the capillary loops at the fingernail bed in 40 cases of diabetic retinopathy and aneurysms were found in only three cases; he found only one aneurysm in 10 brains. These scanty positive findings thus tend to confirm our original report (Ashton, 1949) that the gross micro-aneurysmal formation seen in the retinal vessels is probably not paralleled elsewhere in the body.

An exception must be made in the case of the glomerulus of the kidney, in which aneurysmal dilatations may be demonstrated in association with some of the nodular masses of intercapillary glomerulosclerosis (Ashton, 1950*b*), a disease described by Kimmelstiel and Wilson in 1936 and which is now known to occur almost exclusively in the diabetic subject. The renal lesion cannot be fully discussed here but the study of our post-mortem material has led us to the conclusion that the histogenesis of the glomerular lesion is in every way comparable to the pathological process in the retina. In our series of 110 cases we found that as the retinopathy became more severe the incidence of the nephropathy increased

so that the most severe retinopathies were almost always associated with the renal lesion (Table I). Furthermore, Kimmelstiel-Wilson's disease did not occur in any case in the series without a retinopathy (Table II).

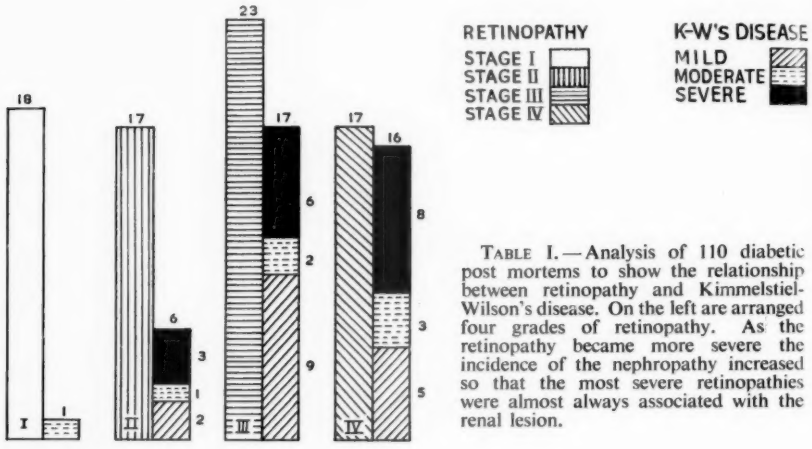

TABLE I.—Analysis of 110 diabetic post mortems to show the relationship between retinopathy and Kimmelstiel-Wilson's disease. On the left are arranged four grades of retinopathy. As the retinopathy became more severe the incidence of the nephropathy increased so that the most severe retinopathies were almost always associated with the renal lesion.

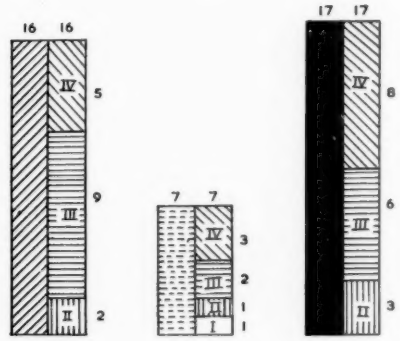

TABLE II.—Analysis of 110 diabetic post mortems to show the relationship between Kimmelstiel-Wilson's disease and retinopathy. The three grades of Kimmelstiel-Wilson's disease appear on the left. In this series the nephropathy was constantly associated with retinopathy but when the two lesions co-existed there was no correlation between their degrees of severity.

As the disease process advances in the retina new vessels begin to form and they arise by an elongation of the existing capillaries, so that loops are formed and this process continues until multiple loops result (Figs. 3, 4, and 5). As long as this new vessel formation remains confined within the retina it appears as closely packed glomerular-like tufts (Fig. 6), but sooner or later it ruptures through the internal limiting membrane and appears as a flat pannus-like network between the vitreous body and the retina (Fig. 7) or, of course, it may actually grow into the vitreous body. Ballantyne and Michaelson (1948) stated that new vessel formation in the retina began by budding; we have not seen this process, but this is not to deny that it may occur.[1]

This type of new vessel formation, with elongation of the vessel wall with looping, is seen also in vascularization of the cornea; it is a type which Swindle (1938) called "vascularization unaccompanied by neo-vasculogenesis". It is of importance in that it opens up another line of approach to the problem of the mechanism of micro-aneurysm formation for it can be seen that at least the loop type of aneurysm could arise by a process of degeneration in a regenerating loop (Fig. 8). There is little evidence, however, to regard all retinal

[1]Since this paper was read we have been able to demonstrate the "budding" process in retinal new vessel formation. Both processes, therefore, occur.

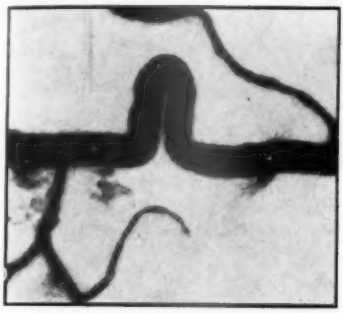

FIG. 3.—Injected diabetic retina. The new vessel formation commences by an elongation in the existing capillary, so that a loop is formed. (× 187.)

FIG. 4.—Diabetic retina injected with Indian ink. Shows further elongation of the vessel. (×187.)

FIG. 5.—Diabetic retina injected with Indian ink. The intra-retinal new vessel formation is extensive and the process of looping is clearly shown. (× 55.)

FIG. 6.—Diabetic retina injected with Indian ink. As long as the new vessel remains confined within the retina it appears as a closely packed glomerular-like tuft. (× 16.)

FIG. 7.—Diabetic retina injected with Indian ink. The new vessel formation has ruptured through the internal limiting membrane and appears as a flat pannus-like network between the vitreous and the retina. The process of looping may still be seen. (× 16.)

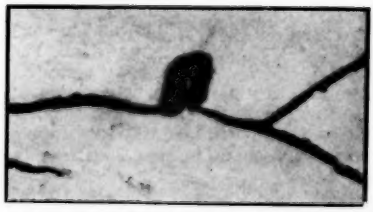

FIG. 8.—Diabetic retina injected with Indian ink. Shows a varicose loop which progresses to the formation of a micro-aneurysm. This type of aneurysm could arise by a process of degeneration in a regenerating loop. (× 195.)

aneurysms of this origin, although many arguments could be advanced in support of such a theory. In any case the idea would advance us little for the basic cause of the aneurysm would still remain unknown.

Before studying the possible causes in diabetes it is first essential to know whether these lesions may be found in non-diabetic subjects.

We have, therefore, carried out an investigation which has involved the examination of 336 eyes from non-diabetic patients and our findings are reported in detail elsewhere (Ashton, 1951). 162 eyes were removed at operation and 174 were obtained at 88 post-mortems. Of those eyes removed at operation where the retinal vessels could be clearly seen after staining or injection, one-third showed micro-aneurysms and they were most commonly found in cases of thrombotic glaucoma and chronic choroido-retinitis.

Of those eyes removed post mortem one-third showed micro-aneurysms. Three of the cases were malignant hypertensives with papillœdema and retinopathy and they showed micro-aneurysms on the venous and arterial side of the capillary network, with fatty degeneration in the vessel walls, exudates and fat-containing macrophages; indeed, the changes were similar to diabetic retinopathy but more acute and less severe.

In 79 of the post-mortem cases in which no eye disease was suspected and in which no gross ophthalmological findings were to be expected in life (that is, what may be considered to be normal eyes) micro-aneurysms were found in 23, that is in 29%. In about half of them the micro-aneurysms were confined to the extreme periphery of the field; they were small and few in number but often indistinguishable from the diabetic type of aneurysm. The cause of their origin and the reason for their anatomical distribution are unknown. Capillary aneurysm formation in the retina has thus been found to be of frequent occurrence and it is clear that, apart from vascular sclerosis, the occasional capillary micro-aneurysm is the commonest pathological lesion in the retina.

The finding of micro-aneurysms in such a high percentage of normal and pathological eyes is suprising and it is difficult to elaborate a single theory which will explain the histogenesis of these lesions in each of the conditions in which we now know them to occur.

If it is true that they arise in focal areas of degeneration in the vessel wall, it is not difficult to explain the histogenesis of these lesions in thrombosis of the central retinal vein or in malignant hypertension for in both cases a degeneration might easily result from anoxia and engorgement, in the first case from venous occlusion and in the second from arteriospasm.

In chronic uveitis the vascular degeneration may be a secondary effect of the toxic products of the uveitis itself, and in diabetes we may postulate, as Ballantyne did (1946), that there is some circulatory toxin, a by-product perhaps of the abnormal metabolic process, which is highly selective for the retinal capillaries. No such toxic substance has, however, been demonstrated and those substances which are present in abnormal quantities in the blood of the diabetic, such as glucose, ketones and lipoids, etc., cannot be clearly related to the onset of retinopathy and thus the theory of a selective toxic substance as a causative factor becomes an increasingly disappointing one.

It is, therefore, tempting to speculate further on the nature of the retinal vascular changes, and our numerous findings point to the same conclusions which Friedenwald (1950) has recently advanced. That is, that the muco-polysaccharide protein complexes within the vessel walls are in some way involved in the diabetic defect.

Jacobs (1949), by measuring bound glucosamine in the serum, has recently found that the muco-polysaccharide of the mucoid fraction of blood plasma is markedly increased in the diabetic subject and that the figures run parallel with the glucose level and are similarly reduced with insulin. He concluded that the glucose anomaly in diabetes is but one manifestation of insulin deficiency and that perhaps this phenomenon is another. It is too early to hazard a guess as to why these mucoids should be withdrawn from the vessel walls in some areas and deposited in others, as in the glomerulus, but the problem is now clearly one for the biochemists and future advances in this field can be expected only by close collaboration with them.

ACKNOWLEDGMENTS

I would like to express my thanks to the surgeons of the Moorfields, Westminster and Central Eye Hospital for the provision of the material and for the clinical details they have supplied. I am also most grateful to the many pathologists and physicians who have co-operated in this work. I am indebted to Dr. Peter Hansell for the photographs and to my technicians, Mr. G. Knight, Mr. A. McNeil and Mr. D. Bedford.

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Dr. T. H. Whittington said he desired to speak briefly on some aspects of the problem from the point of view of a clinical observer of the diabetic eye. First he stated that the chronic, so-called mild, apparently fit diabetic, with a high renal threshold, was particularly prone to retinopathy, and therefore a negative urine should not satisfy a competent ophthalmologist; second, that early adequate control, persistently adequate, considerably lessened the likelihood of diabetic retinopathy. Even when diabetic retinopathy was well established, such persistent adequate control might markedly lessen the retinal signs. An apparently healthy, heavily built, man of 52, first seen in February 1946, was found to have typical and gross retinopathy. At the Diabetic Clinic at King's College Hospital he was stabilized by diet, and insulin. Ten months later both the appearances in his fundi and his vision were much worse. It was then that the picture (Fig. 1) was painted. This shows innumerable hæmorrhages

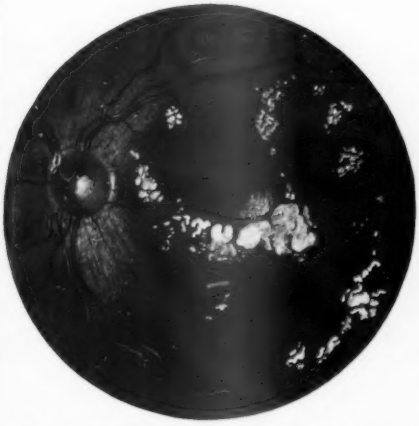

FIG. 1.—December 1946: Gross and typical diabetic retinopathy with hæmorrhages of all types, diabetic exudates, and massive deposits at the macula.

[Hamblin.]

FIG. 2.—August 1950: Disappearance of all hæmorrhages, and of the massive waxy deposit at the macula.

of all diabetic types, the whitish diabetic exudates with their characteristic distribution, and also, what had not been mentioned so far in the discussion, massive solid-looking waxy exudate at the macula. (The other eye was much the same.) At this date (October 1946), ten months after the start of treatment, Dr. W. G. Oakley reported—"He has been well controlled ever since he was at King's last February, and his B.P. has never been raised". Blood pressure was 150/80.

Figure 2 was painted four years later, when a very marked change was noted. It shows that only one hæmorrhage was left of the innumerable diabetic hæmorrhages which had been so obvious at the earlier stage. The characteristic whitish diabetic exudates have largely disappeared, and the gross waxy-looking exudate at the macula is no longer present, a greyish white flat area of smaller size representing it. Dr. Oakley now reported—"Diabetes consistently controlled, but with progressive increase in albuminuria and hypertension. The case is now one associated with Kimmelstiel-Wilson disease of the kidneys and I am afraid the outlook is not good". Blood pressure was now 160/100.

In January 1951 a few months later, the fundi were the same, except that the right fundus showed a few small hæmorrhages. The report at this date was—"He has kept his diabetes extremely well controlled ever since I first stabilized him in 1946, but I regret to say that he has an increasing albuminuria and a rising blood pressure, which is now 190/110".

Summary: This case, carefully watched for over five years, shows: (1) that a gross diabetic retinopathy might at first increase during adequate control; (2) that with continued adequate control, profuse retinal hæmorrhages could completely disappear and large deposits be absorbed; (3) that retinal lesions might be very extensive without any signs of vascular disease, or hypertension, and (4) that despite increasing renal disease and rise in tension, a gross diabetic retinopathy might much diminish under constant control.

Dr. M. Mencer Martin said that in 1924 E. Gräfe reported the disappearance of a diabetic retinopathy with an increase in the intra-ocular tension in that eye (*Ber. dtsch. ophthal. Ges.*, **44,** 53), the other eye had been glaucomatous for a long time and in it diabetic retinitis never developed. This suggested some connexion between intra-ocular tension and the development of a retinopathy and led the speaker to carry out measurements of intra-ocular tension over twenty-four-hour periods both in diabetic patients and normal controls. While the normal person showed the highest intra-ocular tension at about 6 a.m., which gradually fell during the day and rose again during the night, the tension in the diabetic patient failed to show this diurnal variation. In the diabetic, the tension tended to rise and fall quite rapidly, and though it would have been satisfactory to have correlated it with the level of the blood sugar, the correlation was not obvious in the small number of cases examined. It may be that the wide variations in intra-ocular tension are the local factor predisposing to the development of a diabetic retinopathy in the presence of vascular disease. If experiments were carried out on a larger number of patients, some relationship between the intra-ocular tension and the appearance of retinopathy might be established.

Dr. W. G. Oakley said that he would throw out as a chance clinical observation that among the diabetics he had seen and examined he had been struck by the fact that diabetic retinopathy was uncommon among people with high degrees of myopia, and in those who did show it, it was often milder than usual in relation to the duration of the diabetes.

Section of Otology

President—D. F. A. NEILSON, F.R.C.S.

[*March* 2, 1951]

The Effect of Sympathetic Stimulation upon the Cochlear Microphonic Potentials

By J. C. SEYMOUR,[1] M.B., B.S., and J. W. TAPPIN,[2] B.Sc.

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THE autonomic innervation of the inner ear is a subject of increasing interest to the clinician, but surprisingly enough has received little attention from the experimental point of view. This prompted us at the Ferens Institute to undertake certain investigations, of which the present communication is a preliminary report.

We are, at the moment, confining our attention mainly to the cochlea, and the cochlear division of the VIII nerve, but it is obvious that many of the physiological changes experienced by the former may apply equally well to the statokinetic labyrinth.

When evaluating the experimental effects of sympathetic and parasympathetic excitation, a number of points must be borne in mind. Firstly, that the effects may vary with the physiological state of the tissues. Secondly, that species differences and individual differences within the species are considerable, and hence present an inevitable problem when one attempts to apply animal results to man. A third complicating factor is the extensive anatomical connexions of the cervical sympathetic with the parasympathetic of the facial, glossopharyngeal and vagus nerves on the one hand and the phrenic and cervical spinal nerves on the other. These connexions are well marked in the rabbit and cat—in the latter the vagus and sympathetic trunk actually run together—but particularly so in man, where it was noticed in the dissection of a number of cadavers and the microdissection of a small number of fresh fœtuses that the pharyngeal and cervical plexuses were richly connected with the glossopharyngeal, the carotid region, Hering's nerve, the vagus and the superior cervical sympathetic ganglion. This extensive network has been investigated by Tchibukmacher (1938) in 35 fresh cadavers, and Skoog (1947) has demonstrated the presence of sympathetic ganglion cells on the cervical spinal nerves. The final point of consideration is that in the intact animal the autonomic regulation takes place through reflex mechanisms which are dependent upon afferent stimulation and integration at higher levels of the central nervous system. Just how much anæsthesia affects these higher centre integrations is difficult to assess, but in these, our initial investigations, we elected to give barbiturates as an anæsthetic for reasons referred to later, and have temporarily put on one side this aspect of the problem.

In order to cover as wide a field as possible, we selected the three laboratory animals, guinea-pigs, rabbits and cats, upon which to work, and determined the effect of sympathetic stimulation on the cochlear microphonic potentials. The state of the potentials bears a relationship to the physiological state of the cochlea and to the frequency of the sound source within a range of 20–16,000 c.p.s. in cats, rather less, i.e. 14,000 c.p.s., in guinea-pigs. Their function, however, remains a controversial issue and is not clearly known. They appear to

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be an epiphenomenon of auditory function and though hearing may be lost while the microphonic potentials remain unimpaired, it is never retained in their absence (Covell and Black, 1936) so presumably they must be regarded as an indication of the perception of sound. Their use as an index of hearing, however, is limited. Although it is certain that many of the characteristics of hearing are reflected in the microphonic potentials, this association is not absolute. However, within given limits, a change of loudness bears the same relation to a change in the microphonic potentials as it does to a change in the intensity of the sound stimulus.

The microphonic potentials are influenced by a number of factors, an important one of which is anoxia. Wever *et al.* (1949), in studying the effects of lowered oxygen tension upon cats, noted that the microphonics were greatly reduced after the animals were subjected to periods of oxygen lack and that they did not regain their former value when full oxygenation was restored. Repeated exposures gave a cumulative deterioration of response.

It is also well known that deprivation of blood supply causes a disappearance of the microphonics.

The former observations we have been able to substantiate, in part, on a number of animals. Certainly a falling blood oxygen tension causes lowering of the cochlear microphonics with recovery as re-oxygenation occurs, but we did not subject our animals to prolonged periods of anoxia.

Juul (1944), studying the effects of a number of pharmacological substances, observed that the microphonics were unaffected by salicylic acid, quinine, allopropynal, adrenaline, prostigmin, and urethane anæsthesia. Other investigators have shown that ether does not affect them either until the anæsthesia is so deep that circulation ceases.

We have, to date, not concerned ourselves with the pharmacological aspect, other than to confirm the observations of the effect of adrenaline when administered by the intraperitoneal route, intravenous injection seems to produce a temporary, small diminution, varying with the strength of solution used. At death, the microphonics fall immediately to one-fifth of their value and then are reduced slowly over the next few hours until they finally disappear.

Experimental Technique

With this as the pattern of behaviour of the cochlea, we evolved a technique to study the effect of electromagnetic stimulation of the cervical sympathetic trunk upon the cochlear microphonic potentials. All the animals were anæsthetized with intraperitoneal nembutal and a tracheotomy performed. The bulla on the side to be investigated was then carefully exposed by the standard ventral approach, care being taken to ensure that in the dissection no major vessel was cut or injured, nor a ligature used except on the vessel to the salivary gland. Only enough of the bulla was cut away to facilitate accurate placing of the differentiated electrode on the apical coil of the cochlea in the guinea-pigs and on the edges of the round window in the rabbits and cats, thus preventing, as much as possible, excessive drying or cooling of the cochlea as the experiment progressed.

In order to attain as nearly physiological conditions as possible, the absolute minimum amount of retraction was used, particular care being taken to avoid pressure on the carotid vessels, pharyngeal wall and the nerve trunks. The cervical sympathetic trunk was usually exposed for a distance of about 5 mm. at a level 1 to 1·5 cm. below the superior cervical ganglion, in the rabbits and cats, somewhat higher in the guinea-pigs. The ganglion itself was never exposed or approached until after the completion of the experiments, and then only in confirmation, when the trunk consisted of a loose leash of filaments and had given some difficulty in identification. This detail was observed to ensure that there was no interference with the blood supply of the ganglion, for, as Eccles (1935) has shown, depriving a sympathetic ganglion of its blood supply results in blocking of synaptic transmission, the greater part of the effect occurring within a few minutes, but a few hours being required for the complete block. Similarly, Bronk *et al.* (1938) demonstrated that when the circulation to a sympathetic ganglion is stopped, there is a progressive decrease in the number of cells which respond to single preganglionic volleys; and hence our efforts to avoid the introduction of this conditioning effect upon our stimulation.

The apparatus used in the experiments consisted of a pure tone sound source, a high gain push-pull amplifier to increase the cochlear potentials approximately 100,000 times and a cathode-ray tube assembly to enable them to be shown on a screen. An electrical stimulator was used for exciting the sympathetic trunk and a set of micromanipulators enabled accurate positioning of the silver micro-electrodes. The stimulating probe consisted of two fine silver wires imbedded in a rod of Perspex which had a slit at the tip, in which the sympathetic nerve trunk was placed. By this means only a short length of the trunk was stimulated, and the impulse thus prevented from spreading to other parts of the animal. Movements of the animal's head were avoided by means of a rigid pillar clamp which served for both rabbits and cats.

We had to be certain that the variation in cochlear potentials was produced by the stimulation, and not by any artefacts. By far the most troublesome of these was fluid, which gathered between the electrodes and caused a considerable reduction in the potentials. This difficulty was largely overcome by initial removal of the salivary glands, and thoroughly drying the inside of the bulla before each recording. The variation of electrode contact could have caused some alteration and we tried several types of electrode, and several methods of application. In the initial experiments a pointed stainless steel needle was lowered into a small depression drilled into the wall of the cochlea of the guinea-pigs. Later experiments were tried using a silver wire touching the edge of the round window, but the most successful results were obtained with chloridized silver wire.

Pure sine waves in the frequency range 1,000 c.p.s.–2,000 c.p.s. and of intensity well below human pain level were injected into the animal's ear, and the cochlear potentials picked off, amplified, portrayed on the screen of the cathode ray tube and photographed. The sympathetic trunk of the same side was then stimulated in each animal, and recordings before, during, and after stimulation were taken.

Results

The results appear to be similar for most of the animals studied, though for the purpose of this paper we chose to do a series of 3 guinea-pigs, 6 rabbits and 4 cats.

Almost immediately after stimulation was begun, in a latent period of less than one minute, the microphonics were sometimes observed to undergo a small but appreciable increase in size. This increase, though never more than 1/8 of their original value, and sometimes much less, was quite distinct. On continued stimulation, they remained unaltered for a variable number of minutes depending on the species of animal, about ten minutes in guinea-pigs and twenty to thirty minutes in the others. After this period they underwent a gradual diminution in size with further stimulation, reaching a level, usually in the region of 2/3 their original value, though occasionally even lower to almost 1/2 their previous level. It was noted, however, that there was no distortion of the sine-wave form.

After cessation of stimulation, there was a variable latent period of ten to fifteen minutes before the potentials began gradually increasing in size again, sometimes regaining their initial level, though more often failing to do so by a distinct margin, particularly if it was the second or third occasion of making the observations. In these latter conditions, somewhat naturally, the behaviour of the potentials was in no way as demonstrable as on the first stimulation.

Excessive stimulation on a number of guinea-pigs and, as observed on one cat only, reduced the potentials to 1/2 or less than 1/2 of the pre-stimulation level, with no restoration at all to a higher level, even after prolonged periods of rest. The reason for this is probably an irreversible change in the cochlea, but we await the histological results of sectioning of the temporal bones before attempting to advance an explanation.

At the conclusion of the experiments the animals were intravitally fixed with Wittmaack's solution, some when the potentials had recovered their resting value, others when the potentials were at the lowest level attained, and it is hoped at a later date to obtain some histological material to correlate with the experimental findings.

Discussion

From these preliminary results it thus seems that the sympathetic nerve supply does exercise some measure of control upon the cochlea. The immediate effect of stimulation was observed, in some cases, to be a slight increase in size of cochlear microphonic potentials as already mentioned, and offers some difficulty in explanation. If it is a direct effect upon the cochlea as it seems to be by the short latent period, a pathway for the impulses to reach the cochlea must be envisaged. Two possible pathways are: (1) Via the sympathetic filaments of the plexus in the cerebral blood vessels, internal auditory artery and thence to the cochlea, but the function of these filaments seems to be vasomotor control. (2) Sympathetic pathways from the brain-stem via the VIII nerve to the cochlea. Lorente de Nó (1937) states that the blood vessels of the cochlea are innervated by sympathetic filaments coursing with the auditory nerve, but he describes them as arriving via the facial nerve anastomosis with the carotid nerve plexus. These filaments left the cochlear nerve before they reached the spiral ganglion and passed into the connective tissue which carried the blood vessels. They divided into numerous branches that enveloped the blood vessels with "grape-like" endings but he could not determine how far the filaments accompanied vessels.

Rasmussen (1946) investigating the course and relationship of the olivary peduncle, a bundle commonly mistaken for an auditory reflex connexion between the superior olivary

complex and the abducens nucleus, was able to trace this distinct bundle from the glial-Schwann sheath junction, into the inferior division of the vestibular nerve as far as the ganglion associated with the main saccular ramus. Beyond the ganglion, the bundle passed into Oort's vestibulo-cochlear anastomosis, formerly believed to be a group of aberrant cochlear fibres, and accompanied the blood vessels of the cochlea over a half turn of the basal coil subdividing *en route*, the tiny branches passing towards the ganglion cells. Technically it was impossible to trace the filaments any further. He also described a cochlear-saccular anastomotic bundle, probably that described originally by Hardy, but the morphological features of these bundles suggested them to be visceral efferent fascicles to the cochlea and saccule, though they might equally well contain visceral afferent fibres also. Rasmussen, himself, suggested that they might be parasympathetic fibres supplying the cochlear blood vessels and/or the secretory epithelium overlying the stria vascularis. The bundles themselves, from the comparative anatomical point of view, are well marked in all the higher mammals. If this is the efferent pathway by which our stimulation was affecting the cochlea immediately then the afferent pathway must be considered. As Fulton (1930) has pointed out, ever-increasing clinical evidence seems to point to sympathetic afferents entering via the grey rami communicantes; thus our stimulation on the cervical trunk may have resulted in stimulation of such postulated afferents.

The delayed effect experienced by the cochlea was probably due to the diminution of blood supply as a result of vasoconstriction of the intracranial blood vessels, on sympathetic stimulation. The evidence in support of this control is considerable, dating from the early papers of Forbes and Wolff of 1928 and the literature on the subject since is voluminous. The time taken for the phenomenon to show in our experiments, with some degree of recovery on stopping the stimulation, supports the suggestion, but unless the vessels themselves were directly observed it would be difficult to determine whether the internal auditory artery and its branches were actually in spasm or whether the artery was merely experiencing the effects of spasm of the parent trunk.

Autonomic Imbalance

The concept was first recognized by Van Noorden as early as 1892 but the clinical concepts were first formulated by Eppinger and Hess in 1909. Wenger in 1941 proposed a re-statement of their theory which was mainly to the effect that the differential chemical reactivity and the physiological antagonism of the adrenergic and cholinergic branches of the autonomic nervous system permit of a situation in which the action of one branch may predominate over that of the other. This predominance, or autonomic imbalance, may be phasic or chronic, and may obtain for either the adrenergic or the cholinergic systems. In briefly considering the hypothalamus, the centre of the integration of autonomic impulses, it is worth observing that this region is the most richly vascularized region of the whole brain. Further, capillary counts indicate that the anterior and medial portions of the hypothalamus, including the anterior portion of the paraventricular nuclei, the area to which parasympathetic activity is usually assigned, is two to three times more richly supplied than the lateral and posterior nuclear groups whose assignation is sympathetic activity (Finley, 1940; Cragie, 1940). On this alone it does appear hypothetically possible that the sympathetic nuclei would suffer the effects of vascular spasm before the parasympathetic nuclei and hence produce the entity of autonomic imbalance, but it leaves the question of the ætiological factor for the vascular spasm unanswered.

In comparative studies Campbell (1939) has shown that there are very much wider variations in vascularity among the thalamic and hypothalamic centres in the monkey than the cat. In our experiments we have used nembutal as an anæsthetic, for as Fulton, Liddell and Rioch (1930) and Masserman (1937) have shown, barbiturates produce a state akin to normal sleep and the site of action is chiefly upon the hypothalamus and to some extent the medulla. Thus any reflex phenomena we may observe is through autonomic centres in the brain-stem below the level of hypothalamus.

Relationship of Autonomic Disorder to Ménière's Disease

In evaluating our results and aligning them with clinical experience, we observe that sympathetic stimulation produces diminution of cochlear potentials and hence diminution of hearing within the range and conditions of our experiments, but in no way distorts the form of the sine wave of the potentials. If sympathetic hypertonus is to be considered as an ætiological factor in Ménière's disease, the deafness during the attacks might thus be accounted for.

In answer to the question of the vertigo of Ménière's disease, sometimes severe and sometimes not so marked as the cochlear symptoms, an unequal vascular distribution between cochlea and vestibule has been shown anatomically, and advanced as an explanation.

It is worth noting also the work of Snider and Stowell (1944) and Hampson (1949), who describe the representation of both cochleæ in the mid-line lobulus simplex and tuber vermis of the cerebellum. They noticed that these responses to sound were abolished when the VIII nerve was sectioned or the cochlea destroyed. Further stimulation of the sensory auditory areas of the cerebral cortex evokes responses in the lobulus simplex and tuber vermis indicating a pathway connecting the two areas.

Winkler demonstrated that nerve fibres from the maculæ of the utricle and saccule terminate only in part in the vestibular nuclei, another portion terminating the ventral part of the ventral cochlear nucleus. From the latter the trapezoid fibres proceed to the superior olivary and trapezoid nuclei of the same and opposite sides and thence to the lateral lemniscus where impulses are ultimately projected to the cerebral cortex, the lateral lemniscus being thus a link in both auditory and vestibular cortical pathways.

Histology

In the classical description of the histological picture in Ménière's disease given originally by Hallpike and Cairns (1938) and substantiated by Lindsay (1942, 1944) and many others, gross dilatation of the scala media and certain degenerative changes in the organ of Corti were demonstrated. On one animal of Wever's series, which had been intravitally fixed after being subjected to severe oxygen lack and which had demonstrated impairment of cochlear responses, they noted on microscopical examination of sections that there were marked pathological changes in the organ of Corti over the whole length of the cochlea. The sensory structure had largely lost its differentiated character and was reduced to a misshapen mass in which all nuclei were present, but no cell boundaries could be made out. The arch of Corti could be seen though it was greatly modified in form. No hair cells could be surely identified, though certain nuclei were present that may have belonged to the inner hair cells. On the other hand, the internal sulcus cells and stria vascularis remained in fairly good condition. Reissner's membrane was greatly ballooned out and through most of the cochlea was closely adherent to the wall of the scala vestibuli.

Though only described for the one animal the similarity with the description of the sections in Ménière's disease is remarkably striking. Our own histological material is not yet available for examination because of the time required for decalcification and preparation of the temporal bones.

Summary

Electrical stimulation of the cervical sympathetic trunk is found to decrease the magnitude of the cochlear microphonic potentials, using pure tone stimuli between 1,000 and 2,000 c.p.s. This reduction in magnitude of the potential is unaccompanied by any change in their sinusoidal wave form. The decrease of the potentials is probably due, in part, to diminution of the cochlear blood supply resulting from vasoconstriction. The decrease of the potentials is sometimes *preceded* by a small but appreciable increase. The possible mechanisms for this increase are discussed.

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Sympathectomy in Relation to Ménière's Disease, Nerve Deafness and Tinnitus. A Report on 110 Cases

By E. R. Garnett Passe, F.R.C.S., F.A.C.S.

By way of introduction to this subject I wish to refer briefly to two previous papers. The first by Seymour and myself in 1948 in which we drew attention to the effect of stellectomy on 12 cases of Ménière's disease, nerve deafness and tinnitus. The results were sufficiently satisfactory to encourage us in the further investigation of the possibilities of establishing a treatment of Ménière's disease, which if it did not restore the patient to complete normality might do away with the necessity of absolute destruction of the organ of hearing and balance. Some observations we made have been proved, some disproved, and some greatly elaborated. For instance we now perform a routine pre-operative novocain block which does give us an indication of the effect of the operation.

In this first paper we stressed the direct control of the sympathetic on the blood vessels, but in this present paper I would like to stress the possibility of a central control of the peripheral organ by way of the sympathetic.

The second paper read at the International Congress in 1949 was based on the results of sympathectomy in 44 cases which again bore proof of the promise of help which we could offer the majority of cases by intervention in the intracranial sympathetic supply. I use the word *intracranial* and not just *sympathetic supply* to the internal ear. Further investigation of the results has led me to alter my operation site from the neck to the upper thoracic cavity.

In the first paper the blood supply to the inner ear was described in detail together with the sympathetic distribution of the postganglionic fibres along the vessel walls.

At this point it might be opportune to refresh our memories of the reflex paths of the autonomic system, especially the preganglionic fibres. For *all* physiological functions are under a delicate balance of reflex control. This reflex action of the autonomic nervous system is essentially involuntary, but by no means independent of influence emanating from the cerebral cortex.

Anatomy and Physiology

First, the cerebrospinal autonomic reflex arc in the upper thoracic area.

It is composed of paravertebral ganglia and their interconnecting strands of fibres. One ganglion is associated with each spinal nerve (Fig. 1).

Preganglionic fibres emerge from a sharply defined region of the spinal cord. From the first thoracic to the third lumbar segment each anterior root carries medullated preganglionic fibres, which are axons of cells located in the lateral grey horn of the cord (this area is known as the intermedio lateral cell column) (Fig. 2). The myelinated fibres leave the anterior primary ramus as fine bundles called the white rami communicantes and join the sympathetic trunk. They may end in the immediately adjacent ganglion, or they may course up and down to reach the ganglia of the cervical, lumbar or sacral regions. They all end, however, around post-ganglionic neurones in the ganglia of the thorax, neck, head or lumbar regions. In each ganglion whether in the thoracic or cervical region there are ganglionic cells termed post-ganglionic cells, a single axon of each of these cells is known as a post-ganglionic fibre. These fibres pass along visceral somatic nerves, and the small branch by which they reach the somatic nerves is called the grey ramus communicans as they contain little or no myelin. They are distributed to visceral structures, stomach, gallbladder, lungs, joints, &c., whilst others are distributed to blood vessels, mucous, salivary and sweat glands, etc. These pre- and post-ganglionic fibres compose the efferent side of the autonomic arc.

Preganglionic fibres probably do not pass through the superior cervical ganglion into the nerves arising from it excepting those that reach the sympathetic ganglia on the internal carotid and cerebral arteries (Kuntz, 1947).

The afferent side of the sympathetic cerebrospinal arc is comprised of afferent fibres from organs of the body which transverse the sympathetic nerves and enter the spinal cord via the posterior nerve root having a cell station in the posterior root ganglion.

The preganglionic efferent and the afferent fibres which make up the cervical internodal rami enter the sympathetic trunk via the white communicating rami of the upper V or VI thoracic nerves. And, this may be important to the subject under discussion, Ranson and others (Ranson and Billingsley, 1918; Blier, 1930) state that above the superior cervical ganglion there are no afferent fibres, only efferent. Therefore a reflex spinal arc is not possible unless it originates in the higher centres, or the spinal cord itself.

Autonomic centres are present in the medulla and pons (Owsjannikoff, 1947). This area was recognized as a vasoconstrictor area as early as 1871.

Diencephalic nuclei known to be functionally related to the autonomic system are located mainly in the hypothalamus and from these nuclei descending fibres pass into the intermedio-lateral column of the spinal cord from which, as I have explained, the preganglionic sympathetic fibres originate. Some of the fibres cross and some do not.

Now the lateral hypothalamic area is rich in *afferent* fibres from the whole body including the higher centres, especially from neurones in the frontal lobe of the cerebral cortex. Hence we may envisage the profound effect that the higher centres may have on the autonomic system.

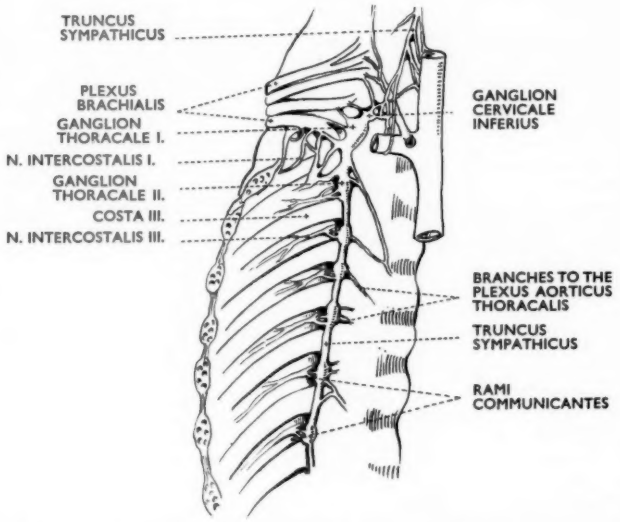

FIG. 1.—Right paravertebral ganglia and their connexions with spinal nerves. (After Spalteholz.)

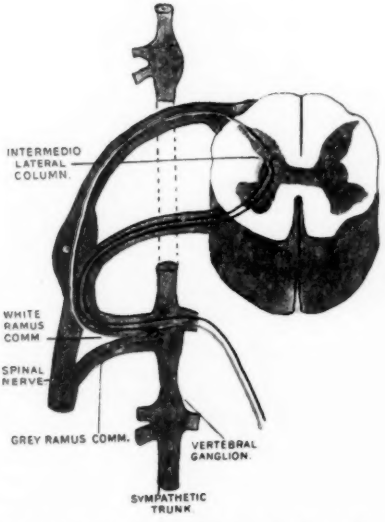

FIG. 2.—Diagrammatic representation of viscera and somatic sympathetic arcs.

It may not be out of place to draw attention here to the psychological overlay in cases of Ménière's disease. We must not, of course, forget to mention the cranial autonomic nervous system, and I would in particular draw your attention to the fact that the peripheral cell station in the cranial autonomic system *always* lies *near* its organ of distribution. The cell station nearest the ear is of course the geniculate ganglion. All otologists are familiar with the clinical signs of deafness, giddiness and tinnitus, which are associated with herpes of the geniculate ganglion. I feel that its direct influence on the cochlea and labyrinth has been greatly neglected. We are hoping to carry our research further with this ganglion.

A brief word concerning the physiology of the autonomic system. There are considerable data (Claude Bernard, *see* Kuntz, 1947) strongly suggesting that under certain conditions reflex actions are carried out through the ganglia of the autonomic system.

If an efferent sympathetic nerve is stimulated constriction of blood vessels takes place over an area corresponding to the distribution of one to four grey rami above the level at which the stimulus was applied, e.g. arthritis of the cervical spine may cause constriction of the cranial vessels.

All blood vessels are innervated through the sympathetic nerves, but in the head they are also innervated through the parasympathetic nerves, and I would like to suggest the possibility of the parasympathetic by way of the geniculate ganglion being concerned in the innervation of the blood vessels of the internal ear—as well as the sympathetic from the second to the fourth thoracic ganglia. In fact it is known that stimulation of the facial nerve at the geniculate ganglion causes dilatation of the pial vessels and according to Schmidt (1950) the cerebral vessels are in a state of tonic dilatation rather than of tonic constriction as are the vessels of the rest of the body. The demonstration that cerebral vessels can vary their calibre provides a physiological basis upon which temporary disturbances in cortical function may possibly be explained according to Best and Taylor (1950)—perhaps also Ménière's disease by anoxæmia of either the internal ear, or of the cerebral centres concerned. Physiologically we should imagine a balance—on the one hand the sympathetic, on the other side of the scale the parasympathetic. If the scale dips on either side we have a state of sympathetico-tonia (or sympathetic dominance), or a parasympatheticotonia (parasympathetic dominance). Most individuals show a perfect balance when resting, or when there are no afferent impulses from diseased organs, or the cerebral cortex to upset the balance. The blood vessels are in a state of tonus, and there is a reciprocal action of the sympathetic and parasympathetic controlling this tonus.

Before leaving the anatomy and physiology of the autonomic nervous system I should like to stress again the part played by the cerebral cortex in so far as the blood vessels are concerned. Worry is accompanied by peripheral vasoconstriction. It is common knowledge to all otologists that worry brings on attacks of Ménière's disease. Joy and tranquillity cause peripheral vasodilatation (Kuntz, 1947, p. 97). In every case of bilateral cervical or upper dorsal sympathectomy that I have performed the most pronounced feature is a mental change in the patient from one of worry and apprehension to that of tranquillity and a sense of well-being.

Further Experimental Data Concerning the Vascular Supply to the Internal Ear

Has the carotid sinus any influence upon the internal ear? Aring (1945) states that there is a cerebral type of hypersensitive carotid sinus which may cause local vasospasm within the cranial cavity. Weiss and Baker (1933) describe the mechanism of the carotid sinus reflex in relation to cerebral circulation. On stimulation of a hyperactive carotid sinus there is a distinct drop in the oxygen content in the venous blood indicating a slowing of blood through the brain.

Agazzi (1945) states that the existence of nerve fibres in the end cells of the organ of Corti was proved. The particular site and the syncytial formation of these fibres allow the conclusion of their belonging to the sympathetic nervous system.

Montandon (1945) states that lack of histological proof is made up for by abundant physiological proof of its existence.

In my earlier papers I described the results of interrupting the post-ganglionic chain by means of stellectomy. Latterly I have been dividing only the pre-ganglionic fibres from the second and third thoracic anterior roots and the trunk below the third ganglion, for by this means we avoid the enhanced susceptibility to adrenaline of the vessels if deprived of their post-ganglionic sympathetic supply.

According to White (1935) and Smithwick (1949) both adrenaline and sympathin are liberated by stimulation of the hypothalamus. Is it to be inferred therefore that afferent stimulation of the hypothalamus from the cerebral cortex in cases of worry, overstrain, &c. may precipitate Ménière's attacks? If so then pre-ganglionic section, as I am now practising, is preferable to post-ganglionic section.

There can be no doubt that all the data concerning the cerebral circulation must also apply to the internal auditory artery, even more so for the internal auditory artery, is an end artery without collateral circulation. Montandon states that there is no anastomosis between the internal auditory artery and the tympanic vessels. A pre-vertiginous aura was present in approximately 20% of cases and usually took the form of a feeling of fullness in the ear and a dullness of mental activities.

Montandon has described fully the influence of the labyrinth on the vegetative nervous system. He states: "One wonders whether the labyrinth, which can set up circulatory reactions under the influence of rotary, linear, or caloric stimulation, also has a physiological action on the cerebral circulation as well as other important circulatory factors, when the spatial relations of the head are altered."

Concerning the effect of the influence of menstrual periods on tinnitus it was found on interrogation of my patients that 65% said that it made no difference, 30% said that the tinnitus was worse immediately preceding the menses, but lessened during them, and the remaining 5% said that the tinnitus was worse during menses.

With regard to menses and vertiginous attacks there did not appear to be any relation.

TECHNIQUE OF INTERRUPTION OF SYMPATHETIC CONTROL OF BLOOD SUPPLY TO INTERNAL EAR

A. *By local anæsthesia.*—Using 1% novocain without adrenaline a novocain block of the cephalic sympathetic is made either by (1) injecting the stellate ganglion, which is a very simple procedure, or (2) paravertebral injection of the upper 4 or 5 thoracic ganglia (Fig. 9).

Certain interesting observations have come to light in my series of over 100 injections. That there is a vascular tonus—which is controlled by the balance of the sympathetic post-ganglionic fibres and the parasympathetic—is proved by the fact that injection of the superior cervical ganglion or the stellate ganglion by 1% novocain after upper dorsal sympathectomy results in dilatation of the vessels of the tympanum.

It is interesting to note the effect of cervical sympathetic novocain block on the blood vessels of the tympanic membrane. Within sixty seconds gross dilatation of the arterioles occurs (Figs. 3 and 4).

FIG. 3.—Normal appearance of tympanic membrane before novocain block of stellate ganglion.

FIG. 4.—Gross dilatation of vessels of tympanic membrane immediately (within one to two minutes) after novocain block of stellate ganglion.

This dilatation is not limited to the tympanic membrane. Figs. 5 and 6 show the medial wall of the tympanic cavity of a patient before and after novocain block. Furthermore it is interesting to note the advent of gross dilatation of the vessels of the membranous canal and the supporting meshwork, as seen in Figs. 7 and 8, as the result of a procaine block of the stellate ganglion during a fenestration operation under heavy premedication and local anæsthesia in which adrenaline was not used.

Injection of the second, third and fourth paravertebral ganglia after stellectomy did not on the other hand produce any vasodilatation of the tympanic vessels. As this injection was made nearly two years after stellectomy, does it show the complete absence of post-ganglionic regeneration?

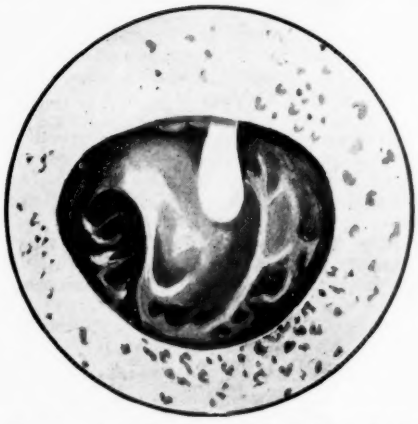

FIG. 5.—Normal appearance of medial wall of middle ear as seen through a large perforation.

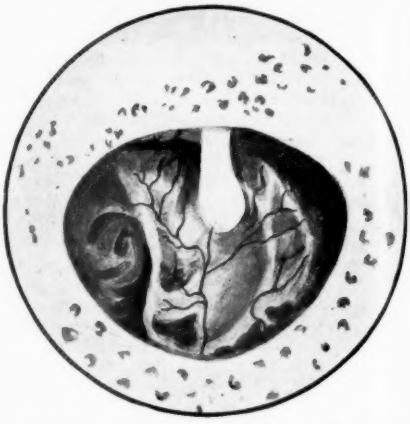

FIG. 6.—Gross dilatation of vessels of promontory and medial wall of middle ear within one to two minutes of novocain block of stellate ganglion.

FIG. 7.—Normal appearance of membranous canal and utricle as seen on fenestration of lateral semicircular canal for otosclerosis.

FIG. 8.—Gross dilatation of blood vessels of supporting trabeculæ and of surface of membranous canal as seen after novocain block of stellate ganglion during fenestration under local anæsthesia (without adrenaline).

Injection of the second, third and fourth thoracic ganglia gives dilatation of the tympanic vessels without Horner's syndrome if thoracic one is avoided. It is not safe to assume from this, however, that there are no vasoconstrictor fibres in thoracic one, though there is no doubt that the majority arise from second, third and fourth thoracic ganglia.

The effect of novocain block on tinnitus.—All sensory nerves carry sympathetic fibres. A few cases of tinnitus have been relieved temporarily by novocain block of the auriculo-temporal nerve. One case in particular was in a young man with a large osteoma of the meatus. Similarly diagnostic injection of the glossopharyngeal nerve and its branches are indicated. Presumably the relief from the tinnitus when it occurs is due to breaking the afferent reflex arc.

Injection of novocain around the neural groove between the fifth and sixth cervical vertebræ in a case of osteoarthritis as shown in Fig. 10 resulted in cessation of the tinnitus. This relief was made permanent by pre-ganglionic section.

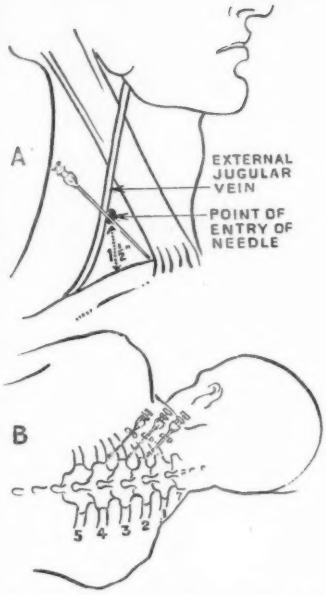

FIG. 9.—Illustrating techniques of A, Novocain block of right stellate ganglion. B, Paravertebral novocain block of upper dorsal sympathetic ganglia.

FIG. 10.—Showing marked arthritic changes around neural groove between fifth and sixth cervical vertebræ. Injection of novocain in this region gave relief from tinnitus.

In a paper on the relief of tinnitus which I read before the French Congress of Oto-rhino-laryngology in Paris in 1949 I advocated the routine blocking of cervical sympathetic and cranial parasympathetic pathways with novocain in an endeavour to locate a nervous reflex arc which might be responsible for the tinnitus. It is surprising how frequently one will discover the reflex. The appropriate treatment then suggests itself.

I have had two cases in whom a mere novocain block was sufficient to stop the tinnitus permanently. Normally of course it only relieves it wholly or in part for periods varying from fifteen minutes to two or three hours. I do not advocate repeated novocain block if the tinnitus returns, but rather surgical intervention. When novocain block produces a temporary or complete absence, or partial lowering of the tinnitus, then I have always found that surgical interruption of the sympathetic does the same.

I have two interesting cases of tinnitus in which hyperthermia produced either by exercise, hot baths, or toxic fevers completely stops the tinnitus whilst the temperature is raised. Is this because of an increase in the blood flow to the internal ear?

Tinnitus to my mind is a peripheral manifestation of a reflex central lesion. How else can we explain its occurrence in an otherwise normal ear. Tinnitus alone is a very rare condition—audiometric tests will nearly always reveal some form of accompanying deafness.

The effect of novocain block on auditory nerve tumour.—In suspected early cases of auditory nerve tumours with unilateral tinnitus and nerve deafness, sympathetic nerve block might well be a useful diagnostic aid, for if the tinnitus is stopped and the nerve deafness improved it is obviously not a case of auditory nerve tumour.

The effect of novocain block on vertigo of Ménière's disease.—I have had the satisfaction of abruptly terminating two cases of Ménière's disease during acute severe attacks by means of a procaine block. One case occurred at the Wembley Hospital. The patient was wheeled into the theatre lying curled up vomiting, with nystagmus, pallor and sweating. 5 ml. of procaine were injected in the stellate ganglion and within three minutes the patient had recovered sufficiently as to walk back unaided to the ward. The other case was similarly relieved in a private house. In neither case did it seem fair to attempt to re-establish the giddiness by a caloric test though no doubt it would be an interesting experiment. Both cases were subsequently subjected to upper dorsal sympathectomy with complete relief.

The effect of novocain block on deafness due to otosclerosis.—There is no effect.

The effect of novocain block on deafness of the perceptive type where there is no apparent clinical cause, but often a family history of deafness.—There is usually temporary improvement most marked in the lower frequencies in early cases up to as much as 30 decibels. In cases of more profound deafness there is usually little or no improvement. I have one striking case of a woman who went suddenly deaf in one ear overnight during an attack of parotitis. The deafness persisted until four months later when after one injection of novocain into the second and third paravertebral ganglia the hearing returned almost to normal and has remained so.

I should like to suggest that it might be worth while performing a sympathetic block in doubtful cases of early otosclerosis. If there is improvement it will be a perceptive deafness, if none, then it is a case of obstructive deafness.

Indications for Operation

Ménière's disease.—Upon carefully establishing the diagnosis of Ménière's disease the patient is submitted to either a stellate ganglion novocain block, or a parasympathetic novocain block. This is a relatively simple diagnostic procedure taking but a few minutes to perform.

As the surgeon but rarely sees the patient in an attack of vertigo, he must perforce rely upon the other two symptoms to guide him, namely tinnitus and nerve deafness. The patient's hearing is carefully tested by audiometry for air and bone conduction immediately before and two minutes, five minutes and ten minutes after the injection. As there is no adrenaline in the solution, and if care is taken not to enter a vessel then no ill-effects are noted, the patient being ambulatory immediately after the injection. There is no need for the patient to be admitted as an in-patient to a hospital for the purpose.

If the tinnitus is subdued or entirely relieved together with some improvement in the low tones for air conduction, then the case is considered to be a suitable one for an upper dorsal sympathectomy (that is a pre-ganglionic section). If there is no improvement, which is extremely rare, then nerve section, or destruction of the end-organ, may be contemplated.

Caloric reactions in a normal person before and after procaine block show no difference.

Caloric reaction before and after procaine block in a quiescent state of Ménière's disease shows no marked difference.

Nerve deafness.—Time does not permit me to elaborate more fully other than to say that primary progressive idiopathic nerve deafness occurring in young people, and usually with a familial history, is more common than one realizes. The careful evaluation of the effect of procaine block on first one and then on the other side is undertaken, and I have found that there is almost always an improvement ranging from 10 to 20 decibels for the frequencies 125, 250 and 500 and perhaps 1,000, rarely 2,000 and never 4,000 or above.

A series of these cases have been operated on—the results will be given later in the paper, but it is perhaps too early yet to form definite conclusions.

Tinnitus.—The investigation of tinnitus has already been referred to. If it occurs without deafness or vertigo, I feel that there is good reason to believe that its origin is central, whether it be of the pulsating, hissing, humming or any other type.

If procaine block temporarily alleviates it, the operation is definitely indicated, but one should warn the patient that the alleviation will reduce it to the same degree as the local anæsthetic.

The patient should be warned that twenty-four hours after operation the deafness and tinnitus may be slightly worse, possibly as the result of irritation of the sympathetic nerve trunk, and that it may take a week or ten days to settle down.

I believe that the only operation for the denervation of the head is the one which gives the best results for the reasons already mentioned, namely, posterior extrapleural upper dorsal sympathectomy as based on the Smithwick operation.

B. *Surgical interruption.—The operation*: [At this point the film of the operation was shown.]

In December last I had the privilege of visiting and discussing the operation with Dr. Smithwick of Boston. It is a modification of his operation of upper dorsal sympathectomy that I now perform and will describe. By leaving the first thoracic ganglion and its pre-ganglionic connexions alone, post-ganglionic cranial fibres are preserved and a Horner's syndrome is avoided. Telford (1935) also advises leaving the white rami communicantes to the first thoracic ganglion intact. It is clearly impossible to remove all post-ganglionic fibres and their ganglia from the cephalic portion of the sympathetic trunk—so perhaps it is better not to remove any, and so avoid the adrenergic factor which I feel may have been responsible for some of the earlier failures. According to James White of Boston (1935)

in explaining why the conventional lumbar ganglionectomy for ischæmic conditions of the foot gave better results than cervico-thoracic sympathectomy for the upper limb, he points out that the *post*-ganglionic fibres to the hand are divided, whilst it is the pre-ganglionic to the foot that are cut, the post-ganglionic fibres remaining intact.

Description of Technique of Operation

The technique used is that described by Smithwick with the modification that I decentralize only the second and third ganglia instead of second, third and fourth as he describes for the upper extremity.

A paravertebral incision is made 7 cm. long and 4 cm. from the spinous processes—the centre of the incision lies opposite the space between the second and third thoracic processes. The fibres of the trapezius muscle are incised vertically and the rhomboid divided obliquely in the direction of its fibres, opposite the third rib, which is carefully determined by palpation. The inner 4 cm. of the rib are removed including the periosteum. The outer centimetre of the transverse process and the underlying neck and head of rib are removed and the pleura gently separated downwards from the side of the body of the vertebræ to the mid-line from a point above the second to below the third rib and laterally to the level of the resected rib end.

The second and third intercostal vessels and nerves are dissected out and traced medially. The third nerve is picked up with a hook and divided at the lateral extent of the incision. It is then traced to the intervertebral foramen dividing the communicating rami running from the anterior aspect of the nerve to the corresponding ganglion. "A dental spatula can then be slipped about the dorsal branch of the intercostal nerve and this is divided. This branch runs vertically and posteriorly between the transverse processes and is given off just lateral to the posterior root ganglion. The latter then comes into view and the spatula is inserted between the anterior and posterior roots at the proximal end of the ganglion. The posterior root is divided with a knife against the spatula blade, leaving the anterior root intact. The arachnoid is then pushed medially with the spatula and separated from the anterior root so that the latter is white and glistening and is free in the foramen. A small spinal fluid leak results. The root is then divided with scissors, so that the lateral centimetre is removed. The proximal end retracts within the canal and after the meninges heal, theoretically it should not regenerate. The second intercostal nerve is treated in a similar fashion. The sympathetic trunk is then palpated. It lies on the anterolateral aspect of the vertebral column exactly where the head of the rib contacts the vertebral body. It is hooked between the second and third ganglia. The second and third sets of communicating rami are clipped with silver clips and divided. The trunk is clipped and divided just distal to the third ganglion and the decentralized second and third ganglia are encased in a silk cylinder to prevent regeneration. The distal end is sutured to the intercostal muscle in the upper portion of the incision.

"The incision is closed carefully in layers with interrupted silk sutures, a catheter having been placed in the extrapleural space. After the wound is closed, any residual air is aspirated and the catheter removed. If the pleura is opened, no attempt is made to close it. Instead, a second catheter is inserted within the pleural space, and aspirated after the wound is closed while gentle positive pressure is used to expand the lung. The catheter is then withdrawn. It is hoped that the precautions taken against regeneration will ensure satisfactory late results."

Results of the Operation

Ménière's disease.—These results include cases from six months to three and a half years.

Table I.—Ménière's Disease (88 Cases)

Duration since operation	No. of cases	Completely relieved	Recurrence of attacks A, Major	B, Minor
3–3½ years	10	7	1	2
2–3 years	13	9	2	2
1–2 years	45	38	2	5
½–1 year	20	18	1	1
Total	88	72 =82%	6 =7%	10 =11%

Thus 93% of cases have remained free from major attacks. It will be interesting to see if pre-ganglionic section will raise this figure still higher. In early cases the hearing has been markedly improved. If the deafness was severe it shows no improvement. The amount of hearing gain that can be expected can be ascertained by audiometric tests beforehand by means of novocain block. It is an interesting fact that bone conduction does not always improve although the air conduction may have done so.

In 5 cases the other ear became responsible for further attacks—these were classed as separate cases in the analysis and the other side was operated upon. During the first three or four weeks in about 10% of cases attacks of varying severity may occur—presumably due to irritation caused by the trauma to the sympathetic trunk, but they gradually pass off.

The patient may need some reassurance during the convalescent stage. I have found that phenobarbitone and ergotamine tartrate are helpful during the first few weeks.

Tinnitus.—16 cases in which tinnitus was the predominating symptom were examined and 13 were subjected to sympathectomy and one to removal of Meckel's ganglion (sphenopalatine ganglionectomy through the posterior wall of the maxillary antrum).

TABLE II.—TINNITUS (16 CASES)

Results Temporarily Obtained by Novocain Block of Sympathetic

Partial relief	8
Complete relief	5
Unaltered	3

The results of the operation for tinnitus were equivalent to that obtained by the pre-operative novocain block. Of the 3 cases in the last group one responded to cocainization of the sphenopalatine ganglion, the ganglion was therefore resected with a permanent cessation of the tinnitus.

In cases of tinnitus associated with Ménière's disease, if the tinnitus was not relieved by the operation, the patients stated almost invariably that the noises no longer worried them.

Nerve deafness.—9 cases were operated upon. These were all early cases of so-called idiopathic perceptive deafness in young people, all had a family history of deafness, and the operation was performed on both sides. The youngest was aged 11 and the oldest 34. All gave an improvement audiometrically with procaine block before operation, and this improvement was obtained and in some cases increased, as the result of the operation. As time is limited this must form the basis of a further paper by which time further cases will have been studied. Severe cases of perceptive deafness including those which did not respond to novocain block were not operated upon.

The criticism that sympathectomy caused stuffiness of the nose was made by Dr. E. P. Fowler, Jr. That there are afferent components of thoracic nerves in the mucous membrane of the nose and paranasal sinuses was observed by Christensen in 1934, but reflex activation of the mucous glands is through the parasympathetic and not the sympathetic which controls the vasomotor reactions. The same applies to ciliary movement—it is under parasympathetic control. On stimulation of the sympathetic the cavernous tissue becomes engorged, but the mucous membrane remains ischæmic, or the cavernous tissue may contract whilst the mucosa is hyperæmic (Steinberg, 1929), or in other words reflex stimulation causing vaso-constriction of the nasal mucosa might prevent emptying of the capillary bed in the cavernous tissue by contraction of the veins which drain it and vice versa for the opposite effect. Recent work by Millonig, Harris and Gardner (1950) with a small series of 27 cases has shown that the amount of nasal engorgement is in direct proportion to the nearness to the nose of the site of bilateral section of the sympathetic nerves. Stellectomy causes less than superior cervical ganglionectomy, and upper dorsal sympathectomy causes little if any change at all in the size of the nasal airway.

CONCLUSION

In conclusion I feel I cannot do better than quote Paterson Ross (1947) who states: "The effect of sympathectomy upon disordered visceral function must be expressed in terms of improvement rather than cure. Even when an operation has been a perfect anatomical procedure, function may not be normal because the severe functional disorder may have resulted in structural disease of the organ."

Sympathetic denervation by a well-planned and correctly executed operation is permanent. In those few cases of failure the advance of structural disease in the organ may have proved to be overwhelming, e.g. Buerger's disease, and this may apply to the vestibular and cochlear organs in certain cases.

It is preferable by anatomical research to determine the resection which will denervate the affected part, and above all to concentrate attention upon the selection of patients for operation so that those may be excluded whose disease cannot be expected to respond to sympathectomy.

Sir James Learmonth (1949) states: "That the remote result of sympathectomy is to obtain for the area a most valuable proportion of the immediate post-operative increase in the blood flow, assessed with due regard to the age of the patient and the pathological nature of the original obstructing lesion."

According to Montandon: "The part played by interrelations between the labyrinth and the neuro-vegetative system now seems so important, both in the physiology and the pathology of the labyrinth, that it seems hardly credible that modern textbooks on labyrinthology still ignore it."

Therefore upon this evidence I present a method whereby the restoration of the aural sympathetic-parasympathetic balance can in selected cases undoubtedly improve the function of both the cochlear and vestibular organs and restore the great majority of patients crippled with Ménière's disease to a useful life.

The following are a few illustrative cases :

Case I.—Ménière's disease. Mrs. C., aged 63.

10.5.48: Deafness commenced six weeks ago with giddy attack of two hours' duration. No family history. Since then repeated attacks of severe giddiness. Medical treatment gave no lessening—patient could not walk unassisted.

Tinnitus +++ in right ear. Loud noises were intolerable as they "jarred her ear".

Vertigo +++. Vomiting with attacks of giddiness followed by severe tinnitus in right ear.

Operation 27.5.48: Right stellectomy with ligation of the vertebral artery.

Post-operation notes—

16.6.48: No giddiness whatever. Tinnitus relieved completely.

21.7.48: Feels much better, has more confidence in herself. No giddiness, no tinnitus. Hearing improved.

10.11.48: No giddiness, no tinnitus. Eyelid improved.

15.5.49: No giddiness, no tinnitus. Eyelid improved. Hearing improved.

26.2.51: No giddiness at all. Tinnitus, slight on occasions. Hearing better. Patient says she is very much better and is very pleased.

Date		128	256	512	1024	2048	4096	
Pre-op. 10.5.48	RAC	50	45	45	50	30	50	
	RBC	25	30	30	35	15	30	with masking
Post-op. 26.2.51	RAC	45	30	45	30	15	40	
	RBC	25	30	50	35	30	55	with masking

Case II.—Ménière's disease. Mrs. L. S., aged 46.

1945: Tinnitus commenced with giddiness. Severe attacks for seven months. Fell to the ground four times. Attacks increasing now almost every two to three days. Commence with roaring in the left ear. Each attack prostrates her for two to three days. Severe injury to elbow in one fall. Treated for two and a half years by salt-free diet, and other medical treatment with no result.

Tinnitus.—Pulsating in left ear with a high-pitched whistle.

Vertigo ++++. Very apprehensive.

Operation.—1.7.47: Left stellectomy. Proved by biopsy.

Post-operation notes—

20.7.47: Giddiness completely gone. Horner's syndrome. Pulsating tinnitus completely relieved. Occasional high-pitched sound.

5.8.47: Tinnitus nil. Feels much better in herself. No anxiety state now.

2.12.47: As above.

2.3.48: Hearing slightly improved. No giddiness.

9.6.49: Has had otitis media in right ear, from which patient has now recovered. No giddiness.

31.3.50: No giddiness, feels well. Has been completely deaf in the right ear since she had abscess in it.

27.2.51: No major attack since operation. Noises completely gone.

Date		128	256	512	1024	2048	4096	
Pre-op. 17.6.47	LAC	55	55	70	75	75	75	
	LBC	20	35	45	55	55	nil	with masking
Post-op. 27.2.51	LAC	65	65	65	70	75	75	
	LBC	25	30	40	45	55	55	with masking

Case III.—Nerve deafness and tinnitus. Miss J. B., aged 46.

Deafness commenced in her twenties. First in the right ear. No previous ear disease.

Family history.—Mother and mother's mother deaf. Removal of polypi and opening of antrum in 1924, 1934 and 1945. First seen by Mr. Passe, 1.2.49. No paracusis. +ve Rinne.

Tinnitus.—Right ear—buzzing and a sense of fullness in both ears, more so in right ear. Twenty years' duration.

Vertigo nil.

Operation.—14.4.49: Bilateral sympathectomy. Right sympathectomy by anterior approach. Left not removed owing to fibrous adhesions and subclavian artery very high.

Post-operation notes—

29.4.49: Hearing improved. No noises. Eyes satisfactory.

16.6.49: No noises. Eyes satisfactory.

19.9.49: Noises none. Eyes I.S.Q. Hearing improving.

12.4.50: No vertigo. No tinnitus. Hearing improved. Nasal polypi to be removed.

Jan. 1951: Patient states: (1) Hearing greatly improved—no difficulty at all in conversation now. (2) Tinnitus completely stopped. (3) Feeling of fullness completely gone, and (4) Patient feels very well.

Date		128	256	512	1024	2048	4096	
Pre-op. 22.3.49	RAC	25	20	20	50	45	30	
	RBC	—	—	40	55	60	—	with masking
Recruitment	LAC	20	20	15	40	45	30	
R 1·8–2·0	LBC	—	—	35	45	60	35	
Post-op. Jan. 1951	RAC	10	5	5	20	25	10	
	RBC	35	20	20	20	65	35	with masking
	LAC	15	10	5	40	30	10	
	LBC	35	15	25	45	45	35	with masking

Case IV.—Tinnitus. Mrs. S., aged 23.

Singing and feeling of fullness in both ears, the left worse than the right, since 1946 when the patient blew her nose while suffering from a cold. Tinnitus severe and constant. Nothing relieved it, worse when she had a headache, would sometimes keep her awake.

22.5.49: Injection of novocain 1% into the left stellate ganglion. Tinnitus ceased on the operating table and has not returned since.

9.2.51: Seen again. Tinnitus nil.

Audiometric test.—Hearing normal for air and bone conduction before and after injection.

Case V.—Ménière's disease. Mr. J. S. K., aged 41.

Attacks of rotational vertigo associated with nausea and severe vomiting. First attack was twenty-five years ago, six months' duration. October 1948 severe attack for one week. Has had attacks, lasting twenty-four hours and more, at intervals since. Attacks came on at any time.

Tinnitus nil.

Vertigo present.

Operations.—8.7.49: Left stellectomy. Divided thyroid axis trunk, vertebral artery very long and narrow. Subclavian artery very high in neck.

16.12.49: Left superior cervical sympathectomy.

Post-operation notes—

18.11.49: Mild attacks of vertigo occur every two to three weeks. Very worried and concerned about condition. Pupil constricted.

16.12.49: Second operation, *see above.*

9.1.50: No giddiness now, or nausea, feels much better on the whole. Hearing improved. No tinnitus.

26.2.51: No giddiness except on extending the neck. Hearing good. Patient states that at some times the hearing is perfectly normal on that side.

NOTE.—Patient was quite unable to work for twenty-two months prior to operation, and was in a very depressed mental state. Since operation the patient has not lost a day's work. Can mount ladders, drive a van, &c.

Date		128	256	512	1024	2048	4096	
Pre-op. 17.5.49	LAC	40	45	60	70	60	60	
	LBC	25	15	35	30	30	40	with masking
Post-op. 26.2.51	LAC	35	40	50	60	50	45	
	LBC	35	35	35	30	40	45	with masking

Case VI.—Ménière's disease. Mr. C. B., aged 67.

29.6.48: Bilateral deafness seven years ago with tinnitus and vertigo. No family history of deafness.

Tinnitus.—Severe in left ear for five years.

Vertigo.—First attack at desk seven years ago. Has periods of attacks and periods of freedom. Fallen once or twice. Vomiting +++. Increased by indigestion and dyspepsia. Conservative treatment of no avail.

Operation.—4.10.48: Left stellectomy, vertebral artery ligated with 4 ligatures.

Post-operation notes—

27.10.48: No giddiness, tinnitus lessened. Hearing improved. Pain in left forearm.

26.11.48: No giddiness. Very slight buzz in left ear. Eyelid up, pupil dilated. Hearing improved.

20.4.49: No giddiness. Slight tinnitus in left ear. Hearing improved. Dyspepsia does not trouble him now.

9.6.49: No giddiness. Slight tinnitus in left ear. Eyelid and pupil satisfactory. Hearing good.

15.10.49: No giddiness. Eyelid up. Hearing very good. Very slight tinnitus. No headaches left side.

27.3.50: No giddiness. Hearing excellent. Tinnitus nil. Slight regurgitation.

12.7.50: Hearing good. Tinnitus nil. Giddiness nil. Headaches nil. (Right œsophageal pouch removed by Mr. Ivor Lewis at Northwood, June 1950.)
19.10.50: Hearing good. Giddiness nil. Tinnitus nil. Headaches very slight occasionally.
26.2.51: Giddiness nil since the operation. Hearing better. Tinnitus nil. Patient states operation has been of great benefit.

Date		128	256	512	1024	2048	4096	
Pre-op. 29.6.48	LAC	50	55	55	65	65	70	
	LBC	30	30	35	25	45	nil	with masking
Post-op. 26.2.51	LAC	25	20	10	20	35	65	
	LBC	30	20	25	25	40	65	with masking

Case VII.—Ménière's disease. Mr. D. L., aged 30.

29.7.47: Left-sided deafness with tinnitus and vertigo of three years' duration. Deafness commenced at the onset of the giddy attacks. Under medical treatment (nicotinic acid) for long periods without relief.

Tinnitus.—Constant high-pitched note.

Vertigo.—Three years severe. Associated with vomiting and increase in deafness.

Operation.—29.10.48: Left stellectomy. Preganglionic fibres of 1, 2, and 3, removed but not stellate ganglion. Vertebral artery ligated twice after stripping sympathetic filaments.

Post-operation notes—
6.11.48: No giddiness. No Horner's syndrome. Hearing better.
24.3.49: Mild attack lasting two days. Hearing worse after attack and has not returned. Some dyspnœa. Continuous tinnitus. Left hand dry. Eyelid and pupil normal.
3.6.49: Much improved. Noises very slight.
26.9.49: Feeling very well generally. Another mild attack of vertigo since last visit, very slight tinnitus occasionally lasting a few seconds only. Hearing not diminished. Left hand still dry.
16.3.50: No giddiness. Noises very slight in left ear. Hearing greatly improved. Inspection of tympanic membrane shows no dilated vessels at umbo.
26.2.51: No major attacks since operation. *Hearing better.* Tinnitus very slight. Headaches rarely. Patient's view, very great improvement.

Date		128	256	512	1024	2048	4096	
Pre-op. 29.7.47	LAC	75	80	70	65	55	60	
	LBC	35	45	30	35	35	30	with masking
Post-op. 26.2.51	LAC	45	40	35	30	25	30	
	LBC	20	25	20	15	20	25	with masking

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Colonel A. G. Tresidder said that he had had the pleasure of seeing a number of Mr. Passe's sympathectomy operations and he had also been fortunate enough to study a number of the subjects. Thus he was in a position to compare the pre-operative with the post-operative condition. What had struck him most forcibly was the great benefit which the patients stated they had received with regard to attacks of vertigo, especially those associated with vomiting. For this benefit they were

extremely grateful, and they seemed not to mind whether the noises persisted or whether their hearing was benefited at all. Nevertheless, in some cases there was no doubt that the tinnitus was also lessened, the attacks were less frequent, and the intensity was diminished. He noticed also that in one or two cases the character of the tinnitus was altered in a favourable direction, so that the patient expressed the view that it no longer worried him and he could really ignore the tinnitus. As regards the deafness some subjects showed an improvement in hearing, not only in air conduction but also in bone conduction. One must realize that any improvement in the hearing must depend on the amount of permanent damage already done to the organ of Corti, and this—at least he thought so—depended on the duration of the disease.

Another point which several of these patients insisted on was that they felt much clearer in the head and that their general health had improved. They were now able, many of them, to enjoy life and to carry on with their ordinary occupations.

He believed that here they had a method of treating Ménière's disease which would make unnecessary such severe procedures as labyrinthectomy.

Mr. W. O. Lodge said that many cures had been suggested for Ménière's disease, and, of course, sympathectomy itself had been a remedy which had been advised in other diseases. Therefore he hoped that members would not be too much carried away by the attractions of one procedure without due regard to other possibilities. He asked Mr. Passe whether the other ear in the cases he had described showed any signs of vasodilatation.

Mr. E. D. D. Davis wondered whether Mr. Passe had observed any change in the nasal mucosa after removing the stellate ganglion. He thought the stellate ganglion probably was too far away to affect the innervation of the mucosa of the nose and there were other sympathetic nerve paths to the nose. The hyperæmia of the tympanic membrane was also interesting, and he would like to know how long it had lasted.

Mr. R. S. Lewis said that since the original Paper by Passe and Seymour in 1948, he had carried out sympathectomy several times and was convinced that it had a very marked effect on the internal ear. He used pre-ganglionic section of the second and third thoracic white rami and approached them by the anterior route. He had done eight of these operations in the last fifteen months; some had been carried out only recently, and though the results were by no means final, he would just like to summarize them. All of them were done for Ménière's disease. 4 had been completely relieved so far as vertigo was concerned and in 2 of these 4 the relief had now lasted for more than a year. 2 of the others had been greatly relieved but still had minor attacks, and in the remaining 2, *after a period of freedom*, the attacks had recurred just as severely as before the operation. The tinnitus usually disappeared but there was a strong tendency for it to recur. In 3 cases the noises were now hardly noticeable; they tended to return a little, at the end of a heavy day, but the trouble was comparatively trivial. In the remaining 5 cases the noises had returned to the pre-operative level. So far as deafness was concerned he had not been able to detect any improvement in any of the cases. One interesting observation he noticed was that in 4 cases the canal paresis which had been present before operation was markedly increased post-operatively. This might give a clue as to the mechanism of sympathectomy in these cases. The same observation had been made in experimental animals by other investigators such as Portmann, Terracol and Brunetti. The operation seemed to have been well worth while in 5—possibly 6—of 8 cases, but he could not really say how long the improvement was going to last.

The President asked whether Mr. Passe had any experience of post-operative brachial pain in these cases; also, it would be interesting to learn what was known about the general health of the patients. He himself had been associated personally with one case. Mr. Passe had made the operation look very easy, and he thought there was no need to be discouraged by the rather terrifying approach. In the case in which he was concerned the patient had a good deal of brachial neuritis, but certainly the vertigo had disappeared. Sympathectomy was obviously such a big proposition that one wanted a clear assessment of the risks of the operation. While it was very successful so far as vertigo was concerned he was rather doubtful about its efficacy concerning the deafness and tinnitus.

Mr. Garnett Passe, in reply, said that occasionally they did get cases in which there was brachial neuritis following stellectomy. This might last for two or three weeks or even longer. This was one reason why he now favoured the upper dorsal sympathectomy. With this method, intercostal neuritis was very rare. He had met surgeons who had performed sympathectomy for Raynaud's disease and they stated that they occasionally had patients with brachial neuritis, due to injury of the brachial plexus. Vitamin B in large doses relieved the condition. Since the extrapleural operation, however, there had been no case of intercostal neuritis at all.

Mr. Lodge had asked if the other ear showed any dilatation. The answer was "No". The vessels of the other ear remained completely normal, and even when novocain was injected intravenously there was still no dilatation of the vessels of the ear-drum. One worker in America had been engaged on intravenous injections of novocain in Raynaud's disease and other conditions and the results may be published shortly.

In answer to Mr. Davis, not much change was observed in the nasal mucosa with this approach. If one examined the nose in a case which did show a reaction one saw the usual vasomotor rhinitis type of appearance of the middle turbinate, but very few patients had ever complained of it at all. The injection of the vessels of the ear-drum was not permanent, persisting only for a few minutes. The injection occurred also at the operation but there again it lasted only for a few minutes.